PVCfreeBloodBag.eu

With financial support from EU's Life+ programme

Economic Feasibility Study

A report within EU's Life+ project PVCfreeBloodBag LIFE 10 ENV/SE/037

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1 Introduction

Blood bags are used worldwide in large volumes and are most commonly manufactured of Polyvinyl chloride (PVC) with a Di (2-ethylhexyl) phthalate (DEHP) plasticiser. DEHP is the most common PVC plasticiser and belongs to a group of materials called phthalates. An advantage of DEHP is that it has a conserving effect on red blood cells. However, DEHP leaks from the bag into the blood which subsequently enters the body on transfusion.

A significant body of research has identified DEHP as toxic to reproduction which means that the transfusion of blood stored in DEHP-PVC bags may lead to reduced fertility and may injure fetuses. For this reason DEHP has been added to the CMR list (Carcinogen, Mutagen and Reproductive toxicant substances) and regarded as a substance of very high concern (SVHC) in the EU. For blood bags intended for red blood cell (RBC) storage there are no acceptable PVC/DEHP-free alternatives available today.

PVC is also on the political agenda including a Green Paper on 'Environmental issues of PVC' at European community level. Concerns include the persistence of synthetic chemicals such as poly-chlorinated biphenyls, the unintentional manufacture of dioxins and furans from industrial processes, the use of heavy metal stabilisers used to protect PVC during processing and concerns surrounding the ultimate disposal of PVC wastes.

A public procurement project was initiated in 2009 by the Jegrelius Institute for Applied Green Chemistry at Jämtland County Council with the aim of stimulating the development of a non-toxic alternative to existing blood bags for red blood cells. The demand is for a blood bag which does not contain any substances known to be harmful the environment or human health while at the same time fulfilling the already existing requirements on performance and safety.

The results of the initial project market analysis concluded that it was too early to progress with a full-scale procurement project. However, the progress made in the project suggested that a commercially viable PVC-free blood bag, that met existing technical and performance standards, could be produced providing the right level of R&D investment was made. The project subsequently obtained EU financing under the Life+ programme (LIFE 10 ENV/SE/037), a European cooperation between industry and healthcare. The project has been running since 2011 and was concluded in June 2017. The objectives of the project are to demonstrate that it is possible to produce a PVC-free blood bag that fulfills the technical and performance requirements, and that it is possible to increase the demand for a PVC-free blood bag.

2 Overview of the Blood Bag Market

2.1 Industry Supply Chain and Dynamics

The manufacture of the unmodified PVC granules is undertaken by large petro-chemical companies. Before PVC can be made into finished products it almost always requires conversion into a compound by the addition of additives such as heat stabilisers, UV stabilisers, lubricants, plasticisers, processing aids, impact modifiers, thermal modifiers, fillers, flame retardants, biocides, blowing agents, smoke

suppressors and optionally, pigments. There is therefore significant integration within the supply chain for the PVC feedstocks and chemical additives. Finally, the manufacture and distribution of goods containing PVCs is fragmented across a large number of globally distributed companies.

The PVC industry is highly competitive and technically mature. Increasing demands on the industry to meet with stricter industrial and consumer regulations have led to investment in R&D and infrastructure to increase yield, reduce cost, increase quality/properties and bring down emissions of VCM. Developments have included new process technology, improvements in process design and new performance additives. There is a strong element of lock-in whereby existing supply chain participants have invested capital in establishing technology, processes and distribution networks.

The scale, commodity nature and need for tightly integrated supply chains mean that the PVC industry is generally dominated by large petrochemical companies although smaller PVC production plants do exist. These large companies wield significant power resulting in resistance to customer and regulatory led change.

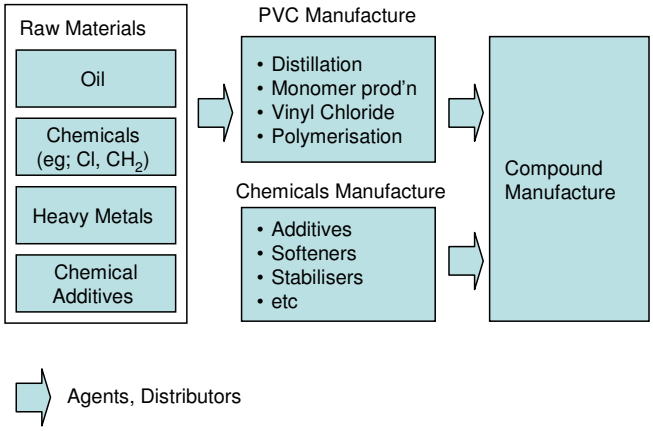

Figure 1: Supply Chain for PVC to Compounding Stage

2.2 PVC Plasticisers

PVC requires plasticisers for most applications. Worldwide six million tonnes of plasticisers are produced annually of which more than 80% are used in PVC. The most common plasticiser in PVC is Di (2-ethylhexyl) phthalate (DEHP), a phthalate. Consequently, DEHP can be detected as a ubiquitous contaminant in the home, workplace and the environment in general. The main source of exposure to DEHP for the general population is dietary, including drinking water, followed by inhalation of air. Food contains DEHP, especially in fat (fish, milk, oils), derived from environmental contamination by this agent and bioaccumulation along the food chain, and from leaching during the process of manufacturing, packaging and storing.

2.3 Do Alternatives Exist?

There have been concerns with phthalates since the 1970's and since the 1980's work has been actively underway to find an alternative to conventional blood bags.

Potential solutions which have been tested include:

- minimising the amount of plasticisers in the PVC
- replacing DEHP with a less toxic plasticiser
- replacing PVC with another plastic
- finding alternative storage solutions
- a combination of alternative plastics and new storage solutions

Alternative plasticisers do exist, but one of them give off a bad smell and create skin reactions in some medical personnel, and others we cannot predict the consequences of. One alternative, using a new storage solution with a polyolefin blood bag has been trialled by the Hoxwort Blood Centre in Connecticut in an attempt to extend the storage time. Results showed that the red blood cells lasted for six weeks using the new systems, which might be sufficient according to the existing needs.

In Stockholm they have actively tried to reduce the amount of DEHP in different blood components. For platelets this has been done by using alternative bags; for red blood cells a large percentage of storage solution has been used and for plasma a shorter storage time.

In the 1980's new plastic materials were introduced which did not contain DEHP, primarily for use with platelets storage. Platelets require continual oxygen supply, in contrast to red blood cells, and the plastic must therefore have a high capacity to let in oxygen. Recently there has been a reduction in the usage of PVC/BTHC bags for platelet storage.

Although replacements have been found for a large variety of medical products, no effective PVC-free material is yet available for widespread blood product usage.

PVC-free alternatives include metallocene-based polyolefin, polypropylene, polyethylene, polyester, silicone, and ethylene vinyl acetate (EVA). In terms of performance and properties, metallocene-based polyolefin most closely competes with PVC plasticized with DEHP. Neither EVA nor the polyesters have gained much acceptance because of limitations to properties and processing constraints in certain areas. Similarly, a variety of polyolefin blends and laminates have found some uses but with limitations.

There is a requirement today to sterile-weld tubing which makes it difficult to replace DEHP-PVC in the tubing. Furthermore, expensive equipment is used today in the blood component production creating a lock-in effect whereby purchasers feel bound to use existing equipment for economic reasons.

No plasticisers have yet been found which provide the same stabilisation properties as DEHP. Alternative plasticisers include citrates, benzoates, trimellitates and adipates. Both Eastman Chemical Company and BASF now supply alternative softeners for use in PVC blood bags intended for red blood cell storage (see Section 2.6 for more details). However, alternative plasticisers will also leach out of the product during medical treatment. Citrates are generally recognised as less hazardous than

DEHP but the potential health risks associated with these alternative plasticisers are not well documented as there is poor toxicological data available.

2.4 PVC in the Healthcare Industry

PVC is ubiquitous in the health care environment. This position has been achieved through a combination of price and product performance, whereby the price is low relative to other alternatives and the versatility and performance characteristics are high. The ability to manipulate its characteristics, through the selection of appropriate manufacturing and fabrication processes and the use of appropriate additives, is unmatched by any other thermoplastic material.

Some of these uses impact directly on patient care whilst others contribute to the overall environment of the patient, including floor and wall coverings and ancillary hospital and clinical equipment. The flexibility and barrier properties of plasticised PVC have resulted in extensive usage as tubes, sheets, containers and coverings.

Of the total use of PVC in the world, it is estimated that a little less than 1% is used in medical devices. There are PVC-free alternatives available today on the market in nearly all areas of use except for blood bags for red blood cells and tubing for haemodialysis. However, it is typical that where non-PVC alternatives are available, suppliers still offer PVC versions alongside.

An analysis of the phase out of PVC within Stockholm County Council in 2005, seven years after the decision to phase out PVC, concluded that there were still large amounts of PVC present in medical devices although clear progress has been made regarding infusion items and products used by neonatal clinics. Worryingly, the analysis pointed to a return to the use of PVC products in some instances, even where non-PVC substitutes were available and had previously been adopted.

There is a general feeling within the transfusion fraternity that substituting DEHP-PVC is a good idea, however, while no alternative exists, the risks are generally overshadowed by the benefits of transfusion medicine.

It is clear from these findings that making the decision to phase out DEHP-PVC from a product is only the first step in the process. A concerted, well organised effort is required often including engagement with the manufacturers to drive the replacement of alternatives.

2.5 Blood Bag Market Structure

There are three distinct levels in the supply chain hierarchy for blood bags. These are the production of the raw PVC, the manufacture of compounds suitable for medical applications and finally the manufacture, assembly and waste management of the blood bags themselves. The competitive and economic aspects of the supply chain vary at each level.

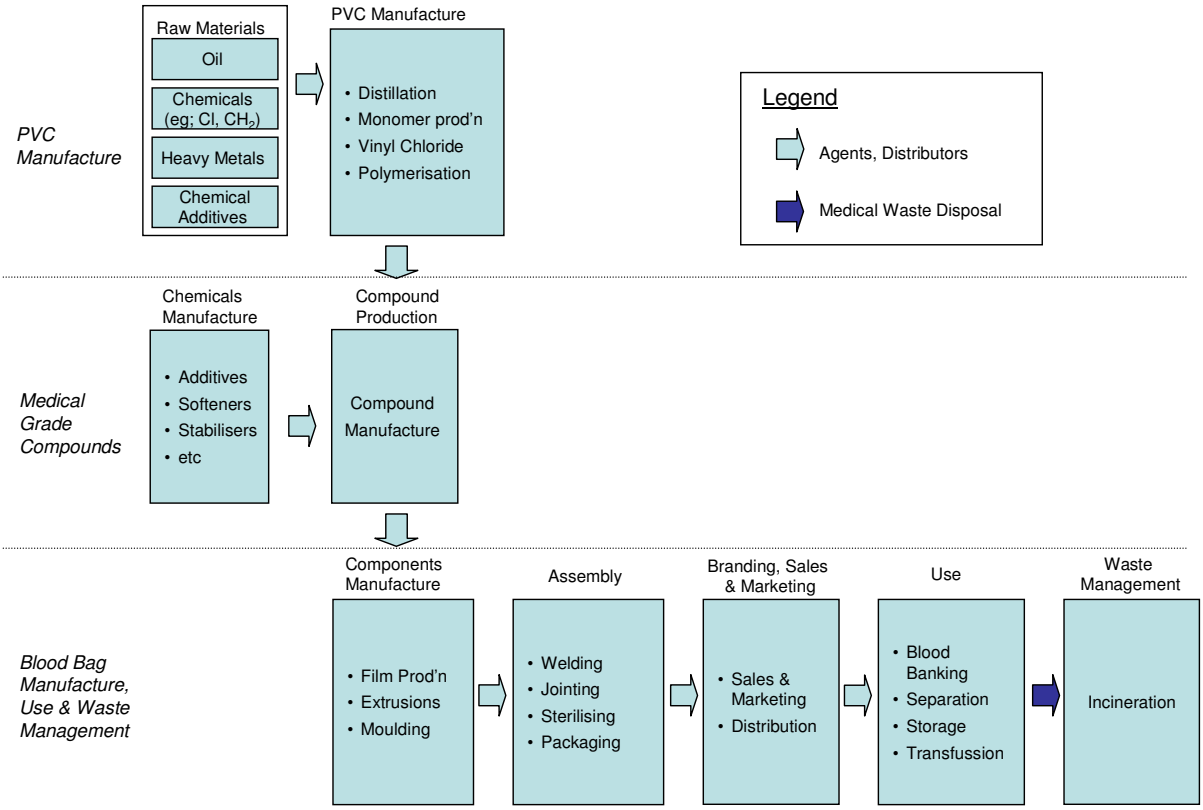

Figure 2: Supply Chain for Blood Bags

The application of PVC to blood bags represents only a fraction of a percent of the total use of PVC globally. As such, the economic impact of substituting PVC from blood bags is not significant at a macro level. However, due to the special requirements for medical PVC (i.e.; purity, documentation) these are typically produced by special compounding companies of which only a few major companies exist in Europe. The specialisation and often customisation required in medical film manufacture means that there are even fewer players at this level.

Resistance from current players, supported by the PVC and chemicals industries, is likely to place a drag on the development of PVC substitutes. Overcoming this resistance is likely to be difficult where the market demand is small or unclear. Anecdotal evidence suggests that this is the case. Suppliers have stated that the larger the market, the more attractive it is for them to engage in the work even if it took a long time. Similarly, many manufacturers operate in a global market making a more international procurement more attractive and easier to justify. A high level analysis of the relative attractiveness to manufacturers of a DEHP-PVC substitute bag has been undertaken later in the report.

The size of the market for a substitute product could clearly be attractive to niche manufactures however the barriers to entry are likely to be significant (an analysis of barriers is presented later in the report). In short, niche players will need to ensure that they can compete against existing global players.

Finally, at the customer level, experience shows that the timeline from demanding a new product to its availability and wide diffusion is a long one. Even so, it is pressure from the end users, typically leading to or supported by legislation, which is likely to be the driving force feeding pressure back up the supply chain.

2.6 Market Trends

Blood bags and their integrated accessories has been the most prolific transfusion device segment for many years. Their widespread usage is due to their instructional simplicity and need for limited donor time commitment. The unit price is also less intensive than automated devices.

Despite this, the market conditions for blood bags have worsened in recent years. A study undertaken in 2002 highlighted healthcare cost-containment, resulting in deepening consolidation and providing end-users with a higher degree of purchasing power, as a key factor depressing sales in the blood collection devices market. Revenues in this segment have also experienced a severe decrease as the number of blood donations suffers a steep decline throughout Europe. Finally, there has been a general trend away trend from blood transfusion towards blood conservation to offset the effects of dwindling stocks and the risks of rejection and disease associated with blood transfusions. Surgeons are increasingly implementing non-invasive surgical techniques and other procedural changes which mean that less blood is lost during surgery, and therefore lower volumes are required for re-transfusion.

A further study undertaken in 2008 concluded that the market in Europe will undergo a profound transformation and experience higher growth rates in the future. This transformation will be led by the continued transition away from manual to automated devices and the development of innovative devices to counter growing concerns related to health and safety issues of blood and blood-derived products. Apheresis and automated whole blood processing devices are poised to replace their manual counterparts over time. In order to secure future competitiveness, significant investments are being made to develop such devices. However, the report concludes that blood bags and their integrated accessories are set to dominate the market for the next ten years and still represent the main revenue stream for many companies. Therefore, product development in the manual blood collection devices segment is continuing, despite its steady decline.

More recently, as a result of increased regulatory scrutiny and consumer demand which has led to a general trend away from DEHP as a softener in PVC in other products, blood bag manufacturers have started to look for alternative softeners for their blood bags. In 2016, Eastman Chemical Company announced that they had successfully completed clinical trials on a replacement softener, DEHT, which has most of the same functional properties of DEHP, including the preservation of red blood cells. Similarly, BASF's DINCH softener is used today in PVC blood bags intended for red blood cell storage. Neither softeners are categorized as a carcinogen, mutagen or reproductive toxicant.

3 The Economic Feasibility Study Purpose and Approach

In order for companies to invest their time and money in the development of a non-PVC blood bag, they need to be certain that it is economically viable to do so. Likewise, the blood bag prototype produced in the current Life+ project needs to be shown to be economically viable if the companies involved are to pursue its further development after the current project ends.

In order to do so, an economic feasibility study ('the study') has been performed. Economic feasibility studies allow the user to assess the economic viability, costs and benefits of a product or service before further financial resources are allocated. The purpose of this study is to find the strengths and weaknesses of a market introduction of PVC-free blood bag (the 'blood bag'), the opportunities and resources required to carry through, and the prospects for success.

The study has been performed by Diffusion Invest Ltd. Diffusion Invest performed the market analysis for the original project and have used that analysis as a departure point for this study.

The study scope is a financial analysis including:

- Estimation of production costs in an upscaled environment
- Estimation of the price for the buyer compared to existing sets of bags (using Sweden as the market example)
- An evaluation of different future demand scenarios based on targeting different market segments (e.g. niche v mass market)
- Various financial performance indicators
- An assessment of the attractiveness and barriers to the development of a non-PVC bag

3.1 Approach to the Study

To determine whether an economically viable blood bag can be produced, an analysis of the supply side and demand side variables has been performed together with a general assessment of the attractiveness and barriers to the suppliers considering producing the new bag.

The supply-side inputs have been primarily provided by the companies participating in the project. The demand side inputs have been sourced from a report produced by Karolinska University Hospital titled Monitoring of Blood Transfusion Operations in EU countries, which was written by Erik Stenholm as an input to the project[1]. These inputs have been supplemented by input data sourced by Diffusion Invest from Internet-based research.

A financial model has been developed (see appendix) to underpin the analysis. The financial model is structured into three component parts. The first, Inputs, contains all of the input data used for the financial analysis. The second, Calculations, contains that the calculations performed on the input data to arrive at the outputs. The third and final part of the model, Outputs, contains the results of the

[1] The link is found here: http://www.pvcfreebloodbag.eu/wp-content/uploads/2016/01/Monitoring-blood-transfusion-operations-in-EU-countries.pdf

financial analysis. These results, together with an assessment of the overall attractiveness to and barriers faced by the suppliers, have then been used to arrive at a set of conclusions and recommendations.

3.2 Input data

The input data consists of five different types of inputs.

1. Key assumptions in respect of Exchange rates Gross profit margins of the manufacturer and the key attributes of the manufacturing process
2. Volumetrics in respect of the number of blood bags in a single set, the current demand globally, for key markets and for Karolinska Hospital (the reference hospital), and finally the percentage demand for high risk patients
3. The current market price of PVC blood bags, based on those procured today by Karolinska Hospital and Ostersund General Hospital
4. The manufacturing costs of the prototype blood bag at different production levels, and
5. The current costs of PVC blood bags. This data has been used to calculate the theoretical market price of a non-PVC blood bag

The sources of the input data and the assumptions for each input are detailed in the financial model and summarised in this report.

3.3 Calculations

Several calculations have been made to arrive at the model outputs.

1. The costs of the raw material inputs, processing and assembly
2. The depreciation costs of the plant and machinery
3. The total cost of the manufactured bag sets, including sterilisation
4. The percentage of the final cost by input type and the breakeven period for the plant and machinery investments
5. Three alternative scenarios have been calculated based on a change in the cost of the raw material and sterilisation input costs
6. The theoretical market price of a PVC free blood bag has been calculated based on the current market price of a PVC bag, adjusted for the differing raw material and manufacturing cost inputs of a non-PVC bag
7. The incremental cost per annum for Karolinska University Hospital if they were to procure the proposed blood bag for either their entire annual demand of bags, or alternatively only for the high-risk patient groups
8. The number of hospitals, with an equivalent annual demand to that of Karolinska University Hospital, required to meet the annual demand assumed in the scenario calculations above

3.4 Outputs

The outputs section of the model contains the summary results from each of the calculations performed in the calculations section of the model. A graphical presentation of the results is also included.

4 The Financial Model Inputs, Calculations and Outputs

4.1 Inputs

4.1.1 Key assumptions

- All costs in € unless otherwise stated
- EUR:SEK = 10
- EUR:USD = 1.13
- Manufacturer gross profit margin = 35%. This margin covers the tax and overhead costs of the manufacturer (e.g. sales & marketing, administration, financing)
- Haemotronics' manufacturing costs are based on a production of 1 million units per annum
- The lead time until first bag could be produced, based on R&D/approvals timeline is 9 Months
- All further pre-production investments (CE marking and plant/machinery) will be capitalised by the manufacturers and depreciated in line with their existing policies
- All bags in the set are made of the same compound
- The welding process is performed with Heat-Welding rather than RF-welding
- A new extrusion line is required (different from the PVC extrusion line used today)
- All plastic components are 'off the shelf' (i.e. purchased, not manufactured)

4.1.2 Volumetrics

The number of blood bags in set, the annual demand for blood bags and the percentage of high risk patients are as follows:

Input	Value	Units
# bags in a set	5	bags/set
Karolinska Volume/Annum	80,000	sets/annum with 5 bags per set
European volume of bag sets used	17,000,000	bags/annum
U.S. volume of bag sets used	21,000,000	bags/annum
Global blood bag demand	112,000,000	bags/annum
Global demand for full sets	22,400,000	sets/annum
High risk patients – Neonatal*	4%	
High risk patients - Neonatal plus cancer/anemia patients**	57%	

*Source: Australian Red Cross

**Source: Australian Red Cross - 4% neonatal, 34% cancer and 19% anaemia

The assumed number of sets produced per annum, used to analyse the manufacturing costs and end-user prices at different production levels, is as follows:

# Sets/Annum	100,000	250,000	500,000	1,000,000

4.1.3 The current market price of PVC blood bags

The market price of PVC blood bags, based on the current prices offered to Karolinska University Hospital and Ostersund General Hospital, are as follows:

Input	Amount	Units
BAT-blodpåssystem from MacoPharma (NPT6280LE)*	113.5	SEK
CompoFlow Select (CQ31450) från Fresenius Kabi**	80	SEK
Fresenius price***	132.5	SEK

Notes

* 5 bag system procured by Karolinska. Includes the lease cost for blood separation press.

** 4 bag system procured by Ostersund. Excluded any equipment lease/purchase cost.

*** Unsuccessful bid in the Karolinska procurement

4.1.4 The manufacturing costs of the new blood bag

The manufacturing costs of the new blood bag consist of the raw material inputs, the cost of manufacturing and the cost of sterilisation of the final blood bag sets. These costs vary according to the volume manufactured, whereby economies of scale can be achieved in the manufacturing process.

The costs have been provided by the companies participating in the project, namely Melitek, Wipak and Haemotronic.

Figure 3: Supply Chain for the prototype blood bag

The costs of the polyolefin granulate have been provided by Melitek. The cost of manufacturing the film has been provided by Wipak. The costs of manufacturing the bags and tubing, procuring the additional components, assembling the bags, and sterilisation by a third party, have been provided by Haemotronics. No breakdown of the component cost for the raw materials and film/tubing manufacturing has been included in the report or model, at the request of the data providers, due to the commercial sensitivity of this data.

The input costs for the raw materials used in the final production process, consisting of the polyolefin granulate price, the manufacturing cost of the polyolefin film and tubing, and the purchase of the components, is as follows.

Input	Amount	Unit
Raw Materials	6.80	€/Set

The price differential between polyolefin and PVC, used to calculate the theoretical market price of the new bag, is as follows:

Input	Amount
PVC Compound Price Increase/(Decrease)	5%

The processing and assembly cost inputs are as follows:

Input	Amount	Units
CE certification cost (one -off)	20,000	€
Plant & Machinery Investment - Extrusion Line Tubing*	300,000	€
Plant & Machinery Investment - Bag Welding Machine**	500,000	€
Plant & Machinery Investment - Assembly Line***	450,000	€
Depreciation period - Extrusion Line Tubing	7.5	years
Depreciation period - Bag Welding Machine	7.5	years
Depreciation period - Assembly Line	7.5	years
Machine Time & Clean Room Cost inc. Assembly (Labour Costs)****	0.99	€/Set
Sterilisation*****	1.51	€/Set
Equipment lease cost******	1.35	€/Set

Notes

* Capacity of 5m sets/annum

** Capacity of 1.25m sets/annum

*** This investment will reduce of roughly €4 the cost of the set. Capacity of 1.25m sets/annum (i.e. at least equivalent to the number of bags welded above).

**** Requires an investment of €450,000. Assumes ISO Class 7 or 8 clean room for all processes. Assumes straight line cost allocation irrespective of volume.

***** Third Party Contractor

****** Based on the price difference between Ostersund (20SEK/bag x 5 bags equivalent) and Karolinska (113.5SEK per set inc. equipment)

A number of scenarios have been modelled based on changes in the price of the film, tubing, components and sterilisation at different production volumes. The following scenarios have been modelled:

Scenario Name	**Scenario Description**
Basic Scenario	All investments and costs are as provided by current manufacturers based on 1m units per annum. Costs increase in line with reduced volume.
Scenario 1	Film, tubing, components and sterilisation prices reduces by 5% for each volume tier from the Basic scenario price
Scenario 2	Film, tubing, components and sterilisation prices reduces by 10% for each volume tier from the Basic scenario price
Scenario 3	Film, tubing, components and sterilisation prices reduces by 20% for each volume tier from the Basic scenario price
Theoretical Market Price	A theoretical market price based on the price differential between PVC and the proposed polymer and the % increase in processing effort for the new polymer versus PVC

The cost reduction for each volume tier and scenario is as follows:

Scenario Price Change	**Production Volume**			
	100,000	250,000	500,000	1,000,000
Basic Scenario	15%*	10%	5%	0%
Scenario 1	-5%	-5%	-5%	-5%
Scenario 2	-10%	-10%	-10%	-10%
Scenario 3	-20%	-20%	-20%	-20%**

**Example:*

The reference cost of film, tubing, components and sterilisation for 1m bags per annum (the Basic Scenario) is €8.31. If only 100,000 bags are manufactured, the cost of the manufacturing inputs will increase by 15%.

***Example 2:*

If the manufacturing volume is retained at 1 million units per annum, but further efficiencies can be realised, for example through in the manufacture of dedicated components, the cost of the manufacturing inputs will reduce by 20%.

4.1.5 The current costs of PVC blood bags

A theoretical market price has also been calculated based on the current price of PVC blood bags in the Swedish market, the price differential between PVC and polyolefin raw materials (bags and tubing) and the manufacturing cost differential between the two different polymers.

Input	**Value**	**Units**
Raw material cost Increase/(Decrease) of Polyolefin versus PVC*	5%	
Production cost Increase/(Decrease) of Polyolefin versus PVC**	42%	
Material cost of PVC sets***	0.9	€/Set
Production cost of PVC sets****	1.2	€/Set
Market Price	10.00	€/Set

* Source: Haemotronics

** Source: Haemotronics

*** based on advertised market prices for PVC blood bags of $0.9 per bag, a raw material input cost representing 30% of the final end price, and each set consisting of five bags

**** based on a market price for PVC blood bags of $0.9 per bag, a production cost representing 40% of the end price, and each set consisting of five bags

PVC blood Bag Price Source: https://www.alibaba.com/product-detail/blood-collection-bag-with-price_60479920849.html?spm=a2700.8239084.botrelate.3.lEuUKp

4.2 Calculations

4.2.1 Production Cost Inputs

The production costs of the new bag consist of the raw material inputs costs, the processing and assembly costs and the depreciation of the fixed assets (production and assembly equipment).

The raw material input costs, at different production volumes, are:

Raw Material Costs per Set (€/Set)	***Annual Production Volume***			
	100,000	***250,000***	***500,000***	***1,000,000***
Raw Materials and Components	*7.8*	*7.5*	*7.1*	*6.80*
Sterilisation	*1.7*	*1.7*	*1.6*	*1.5*
Total Input Costs	***9.6***	***9.1***	***8.7***	***8.3***

The processing and assembly costs, at different production volumes, are:

Processing/Assembly (€/Set)	***Annual Production Volume***			
	100,000	***250,000***	***500,000***	***1,000,000***
Cost/Set	0.99	0.99	0.99	0.99

The annual depreciation of the fixed assets, based on all upfront investments (see Inputs) being depreciated over 7.5 years, is:

Depreciation of Investments	**Amount**	**Units**
Extrusion Line Tubing	40,000	€/annum
Bag Welding Machine	66,667	€/annum
Assembly Line	60,000	€/annum
Total Annual Depreciation	**166,667**	**€/annum**

4.2.2 Total Cost of Production and the Price per Set (Base Case)

The total annual cost of production, at different volumes, and the equivalent unit price per set are:

	Production Volume			
Euros per annum	***100,000***	***250,000***	***500,000***	***1,000,000***
Raw Materials and Components	782,000	1,870,000	3,570,000	6,800,000
Processing & Assembly	99,000	247,500	495,000	990,000
Sterilisation	173,650	415,250	792,750	1,510,000
Depreciation of Investment	166,667	166,667	166,667	166,667
Total Production Cost	1,221,317	2,699,417	5,024,417	9,466,667
Profit Margin	427,461	944,796	1,758,546	3,313,333
Gross Revenue (before tax)	1,648,778	3,644,213	6,782,963	12,780,000
Price per Set (€)	***16.5***	***14.6***	***13.6***	***12.8***
Price per Set (SEK)	***164.9***	***145.8***	***135.7***	***127.8***

An analysis of the cost of each input to the total annual sales revenue confirms that the raw material and the component costs represent more than 50% of the overall end user price.

	Value (@1M units)	**% of Total**
Raw Materials and Components	6,800,000	53%
Processing & Assembly	990,000	8%
Sterilisation	1,510,000	12%
Depreciation of Investment	166,667	1%
Total Production Cost	9,466,667	74%
Profit Margin	3,313,333	26%
Total	12,780,000	100%

A sensitivity analysis has therefore been performed on the raw material and component costs to determine the impact on the end user price from a variation to the input price (see below).

The depreciation of the upfront investment equates to only 1% of the end-user price while the payback on the investment is only 5 months (at 1m units/annum production).

	Annual Production Volume			
	100,000	***250,000***	***500,000***	***1,000,000***
Annual Gross Profit (€)	427,461	944,796	1,758,546	3,313,333
Investment in Plant & Machinery	1,250,000	1,250,000	1,250,000	1,250,000
Breakeven Period (years)	2.9	1.3	0.7	0.4

These investments are essential for production, in the case of the extrusion line and bag welding machinery, and result in a significant reduction in the end user price, in the case of the assembly machinery (€4/set cost saving for an investment of €450,000). Even at low volumes, the cost of the Assembly machinery would pay back in year one. No sensitivity analysis of these investments will therefore be performed.

4.2.3 Scenario Analysis

A number of scenarios have been modelled, based on changes in the price of the film, tubing and sterilisation at different production volumes, to calculate the end-user price at different volumes and with different input costs. The results are as follows.

4.2.3.1 Scenario 1

Scenario one is calculated on the basis of a 5% reduction in the costs of the film, tubing, components and sterilisation versus the equivalent price for the same volume tier in the Base Case scenario.

	Volume			
Input	***100,000***	***250,000***	***500,000***	***1,000,000***
Base Price - Raw Materials/Components	*7.8*	*7.5*	*7.1*	*6.8*
Base Price - Sterilisation	*1.7*	*1.7*	*1.6*	*1.5*
Price reduction - Scenario	*-5.0%*	*-5.0%*	*-5.0%*	*-5.0%*
Scenario Price – Raw Materials/Components	7.4	7.1	6.8	6.5
Scenario Price - Sterilisation	1.6	1.6	1.5	1.4

	Volume			
Annual Cost and Price/Set (€)	***100,000***	***250,000***	***500,000***	***1,000,000***
Raw Materials and Components	742,900	1,776,500	3,391,500	6,460,000
Processing & Assembly	99,000	247,500	495,000	990,000
Sterilisation	164,968	394,488	753,113	1,434,500
Depreciation of Investment	166,667	166,667	166,667	166,667
Total Production Cost	1,173,534	2,585,154	4,806,279	9,051,167
Profit Margin	410,737	904,804	1,682,198	3,167,908
Gross Revenue	1,584,271	3,489,958	6,488,477	12,219,075
Price per Set (€)	***15.8***	***14.0***	***13.0***	***12.2***
Price per Set (SEK)	***158.4***	***139.6***	***129.8***	***122.2***

4.2.3.2 Scenario 2

Scenario two is calculated on the basis of a 10% reduction in the costs of the film, tubing, components and sterilisation versus the equivalent price for the same volume tier in the Base Case scenario.

Input	*100,000*	*250,000*	*500,000*	*1,000,000*
Base Price - Raw Materials and Components	*7.8*	*7.5*	*7.1*	*6.8*
Base Price - Sterilisation	*1.7*	*1.7*	*1.6*	*1.5*
Price reduction - Scenario	*-10.0%*	*-10.0%*	*-10.0%*	*-10.0%*
Scenario Price - Raw Materials and Components	7.0	6.7	6.4	6.1
Scenario Price - Sterilisation	1.6	1.5	1.4	1.4

Annual Cost and Price/Set (€)	*100,000*	*250,000*	*500,000*	*1,000,000*
Raw Materials and Components	703,800	1,683,000	3,213,000	6,120,000
Processing & Assembly	99,000	247,500	495,000	990,000
Sterilisation	156,285	373,725	713,475	1,359,000
Depreciation of Investment	166,667	166,667	166,667	166,667
Total Production Cost	1,125,752	2,470,892	4,588,142	8,635,667
Profit Margin	394,013	864,812	1,605,850	3,022,483
Gross Sales	1,519,765	3,335,704	6,193,991	11,658,150
Price per Set (€)	***15.2***	***13.3***	***12.4***	***11.7***
Price per Set (SEK)	***152.0***	***133.4***	***123.9***	***116.6***

4.2.3.3 Scenario 3

Scenario three is calculated on the basis of a 20% reduction in the costs of the film, tubing, components and sterilisation versus the equivalent price for the same volume tier in the Base Case scenario.

Input	*100,000*	*250,000*	*500,000*	*1,000,000*
Base Price - Raw Materials and Components	*7.8*	*7.5*	*7.1*	*6.8*
Base Price - Sterilisation	*1.7*	*1.7*	*1.6*	*1.5*
Price reduction - Scenario	*-20.0%*	*-20.0%*	*-20.0%*	*-20.0%*
Scenario Price - Raw Materials and Components	6.3	6.0	5.7	5.4
Scenario Price - Sterilisation	1.4	1.3	1.3	1.2

Annual Cost and Price/Set (€)	*100,000*	*250,000*	*500,000*	*1,000,000*
Raw Materials and Components	625,600	1,496,000	2,856,000	5,440,000
Processing & Assembly	99,000	247,500	495,000	990,000
Sterilisation	138,920	332,200	634,200	1,208,000
Depreciation of Investment	166,667	166,667	166,667	166,667
Total Production Cost	1,030,187	2,242,367	4,151,867	7,804,667
Profit Margin	360,565	784,828	1,453,153	2,731,633
Gross Sales	1,390,752	3,027,195	5,605,020	10,536,300
Price per Set (€)	***13.9***	***12.1***	***11.2***	***10.5***
Price per Set (SEK)	***139.1***	***121.1***	***112.1***	***105.4***

4.2.4 The Theoretical Market Price of a PVC-free Blood Bag

A theoretical market price has been calculated based on the price differential between PVC and the proposed polymer and the % increase in processing effort for the new polymer versus PVC.

	Value	Units
Material cost in PVC sets	0.93	€/Set
Production cost in PVC sets	1.24	€/Set
Material cost increase - polyolefin	5%	
Production cost increase - polyolefin	42%	
Total cost increase	0.56	€/Set
Current price per set	10	€/Set
Theoretical market price - Polyolefin Set	**10.56**	**€/Set**

4.2.5 The Incremental Annual Cost to Karolinska Hospital

The incremental annual cost to Karolinska University Hospital, were they to procure the new blood bag, has been calculated. An incremental cost range has been calculated, based on the highest end user price (the base case scenario) and the lowest end user price (scenario three).

	Value	Units
# sets procured per annum	80000	sets
Current price/set	100	SEK
Low price per set (Scenario 3)	105.4	SEK
High price per set (Base Case)	164.9	SEK
All bags replaced		
Current cost per annum	8,000,000	SEK/annum
Cost per annum - Low price per set	8,429,040	SEK/annum
Cost per annum - High price per set	13,190,220	SEK/annum
Cost increase/(decrease) per annum - Low Cost	**429,040**	**SEK/annum**
Cost % increase/(decrease) per annum - Low Cost	5%	
Cost increase/(decrease) per annum - High Cost	**5,190,220**	**SEK/annum**
Cost % increase/(decrease) per annum - High Cost	65%	

An incremental cost range has also been calculated on the basis of the entire annual demand of Karolinska being replaced by the new bag, or alternatively only those bags used for high-risk patients being replaced.

Neonatal Patients Only		
# sets procured per annum	3200	sets
Current cost per annum for sets	320,000	SEK/annum
Cost per annum - Low price per set	337,162	SEK/annum
Cost per annum - High price per set	527,609	SEK/annum
Cost increase/(decrease) per annum - Low Cost	**17,162**	**SEK/annum**
Cost % increase/(decrease) per annum - Low Cost*	0.21%	
Cost increase/(decrease) per annum - High Cost	**207,609**	**SEK/annum**
Cost % increase/(decrease) per annum - High Cost*	3%	

All High Risk Patients

# sets procured per annum	45600	sets
Current cost per annum for sets	4,560,000	SEK/annum
Cost per annum - Low price per set	4,804,553	SEK/annum
Cost per annum - High price per set	7,518,425	SEK/annum
Cost increase/(decrease) per annum - Low Cost	**244,553**	**SEK/annum**
Cost % increase/(decrease) per annum - Low Cost*	3%	
Cost increase/(decrease) per annum - High Cost	**2,958,425**	**SEK/annum**
Cost % increase/(decrease) per annum - High Cost*	37%	

* The % cost increase versus the total annual spend on blood bags

4.2.6 The Number of Hospitals Required to Generate the Target Demand

In order to ascertain the number of customers required to generate the necessary demand at each production volume tier, calculations have been performed using Karolinska as a proxy for an average customer. Calculations have been performed using Karolinska's total annual demand and that for high risk patients only.

Karolinska Annual Demand - All	80,000
Karolinska Annual Demand - Neonatal	3,200
Karolinska Annual Demand - All High Risk	45,600
European volume of bag sets used	17,000,000
U.S. volume of bag sets used	21,000,000
Global blood bag demand	112,000,000

# of Karolinska equivalent hospitals	*100,000*	*250,000*	*500,000*	*1,000,000*
All Patients	1	3	6	13
High Risk - Neonatal	31	78	156	313
High Risk - All	2	5	11	22

4.3 Outputs

The outputs section of the model contains the summary results from each of the calculations performed in the calculations section of the model.

The total upfront investment required to produce the new bag, including CE certification and the investment in production and assembly equipment is €1.27m.

Upfront Investment	**€**
CE Marking	20,000
Plant and Machinery	1,250,000
Total	**1,270,000**

The price per set based on the Base Case scenario, is €12.80 or SEK127.8 compared to the current price of PVC bag set of SEK100 and a theoretical market price for a polyolefin bag set of SEK105.60.

	100,000	*250,000*	*500,000*	*1,000,000*	*% @ 1M units*
Raw Materials	782,000	1,870,000	3,570,000	6,800,000	53%
Processing & Assembly	99,000	247,500	495,000	990,000	8%
Sterilisation	173,650	415,250	792,750	1,510,000	12%
Depreciation of Investment	166,667	166,667	166,667	166,667	1%
Total Production Cost	1,221,317	2,699,417	5,024,417	9,466,667	74%
Profit Margin	427,461	944,796	1,758,546	3,313,333	26%
Gross Sales	1,648,778	3,644,213	6,782,963	12,780,000	100%
Price per Set (€)	***16.5***	***14.6***	***13.6***	***12.8***	
Price per Set (SEK)	***164.9***	***145.8***	***135.7***	***127.8***	

The results of the scenario analysis shows that it is possible to produce the new bag at a price of SEK105.40, if input material and components costs can be reduced by 20% from currently estimated levels at a production volume of 1 million units per annum. Haemotronics have estimated that a 20% price reduction is achievable if the components, which are assumes to be purchased under the current calculations, are produced in house. This would of course require a further investment in the plant and machinery, for which relations have been performed. It does however suggest that the new bag could be produced at a price point very near to existing PVC bags.

	100,000	*250,000*	*500,000*	*1,000,000*
Basic Scenario	164.9	145.8	135.7	127.8
Scenario 1	158.4	139.6	129.8	122.2
Scenario 2	152.0	133.4	123.9	116.6
Scenario 3	139.1	121.1	112.1	**105.4**
Theoretical Market Price	**105.6**	**105.6**	**105.6**	**105.6**
Current Price PVC sets	**100.0**	**100.0**	**100.0**	**100.0**

The incremental cost to Karolinska per annum if they were to purchase the new blood bag varies from a 0.2% increase to a 65% increase, depending on the production volume and cost scenario, and whether they procure the bags only for their high-risk neonatal patients versus their entire annual consumption of blood bags.

Application of bags	*Cost Increase p.a. - Low Cost*	*Cost Increase p.a. - High Cost*	*% Increase - Low Cost*	*% Increase - High Cost*
All Patients	429,040	5,190,220	5%	65%
High Risk - Neonatal	17,162	207,609	0.2%	3%
High Risk - All	244,553	2,958,425	3%	37%

To achieve the required 1m units per annum demand levels, the bags would need to achieve a market share of 0.9% of the total global demand for blood bags, 4.8% of the U.S. market or 5.9% of the European market.

Market Share	*100,000*	*250,000*	*500,000*	*1,000,000*
Europe	0.6%	1.5%	2.9%	5.9%
U.S.	0.5%	1.2%	2.4%	4.8%
Global	0.1%	0.2%	0.4%	0.9%

The following graphs show the cost profile of the new blood bag sets at different volume levels and cost scenarios versus the current PVC blood bags and the theoretical price of a new polyolefin blood bag set. As described above, as the volume approaches 1m units per annum and assuming that a 20% cost reduction can be achieved on the input materials, the cost of the new bag set approaches parity with both the theoretical price and the current market price for PVC sets.

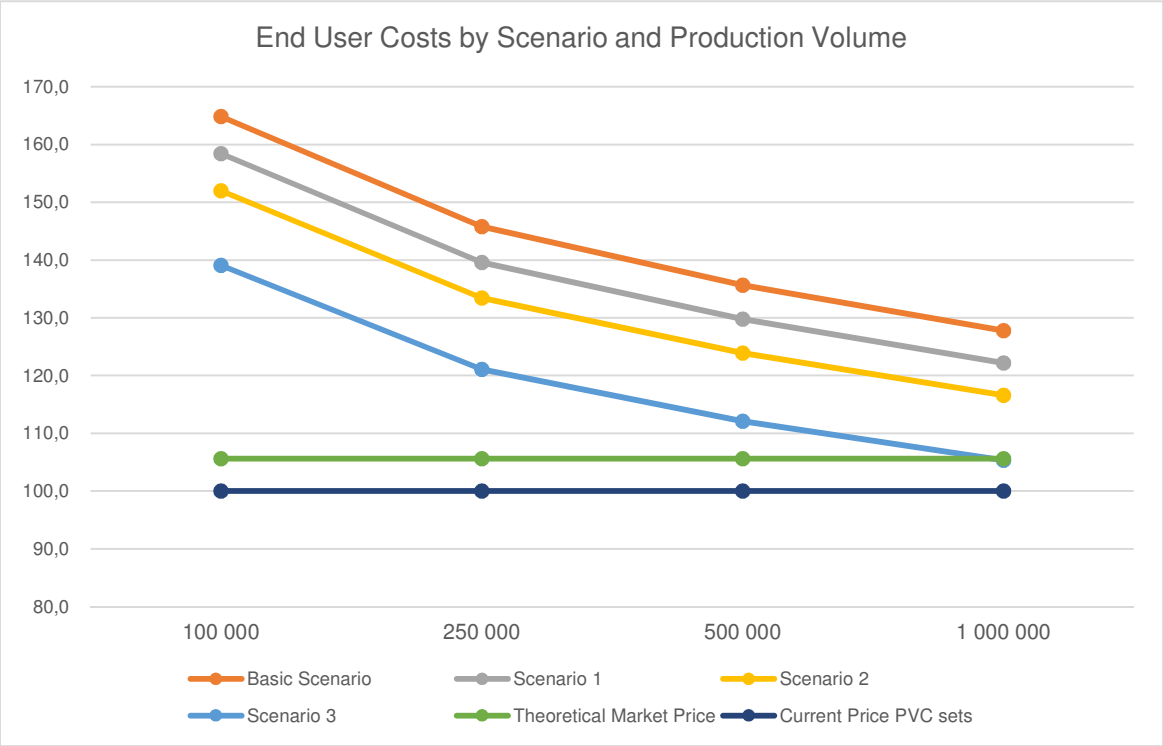

Figure 4: End user costs at different production cost and volume scenarios

5 Analysis of the Attractiveness to Manufacturers of Phasing out DEHP-PVC

There are many factors to consider when evaluating the potential to replace DEHP-PVC in blood bags. At the manufacturing level, these factors may include ease of fabrication, compatibility with other components of a system, performance advantages, or the ability to earn a greater profit while at the same time meeting current and future expected regulations. At the user level meeting regulations, health effects/benefits, product performance, compatibility with existing equipment and cost are the major considerations.

In practice, perfect substitution is difficult to achieve because different materials have different properties and attributes. The commanding market share of DEHP-PVC occurs today because no alternatives have been found which meet the performance criteria, irrespective of cost, namely the ability to preserve red blood cells. Blood bags are a critical, lifesaving technology. As such, finding an alternative is more difficult than traditional substitution where a combination of cost or utility sacrifices can be made or, worse case where the customer is forced to forgo consumption altogether.

Investment in R&D will be required in order to develop an alternative to existing blood bags which is cost competitive across the product lifecycle. Further investment may also be required in capacity building and the development of supply chains. The decision to undertake this investment by manufacturers will be determined by the attributes of the product to be diffused. Furthermore, general risk factors may also have an influence, such as the possibility that economic development may influence the perceived economic risk that a potential adopter faces in the adoption of a technology.

The factors which determine the speed of diffusion of a new innovation were identified by Everett Rogers as relative advantage, compatibility, complexity, trialability and observability. These factors along with general risk factors have been evaluated from the perspective of blood bag manufacturers to understand how motivated they may be to embark on such an investment:

'+' denotes that the factor is positive in the manufacturer's eyes
'-' denotes that the factor is negative in the manufacturer's eyes

Attributes	**Factors**
Relative Advantage	+ Allows companies to demonstrate their eco-credentials in the face of growing criticism and regulation + The development of new patents can provide significant financial return as the market grows + New market with high growth potential for new entrants + Opportunity to reduce CO2 and other emissions which may have a cost under cap and trade mechanisms and polluter pays mechanisms + Incentives and stimulus available in some markets, particularly for bioplastics + May be able to charge a premium to existing products + Alternative polymers are 10-20% more expensive, but are cost competitive due to less material needed for the same size and kind of bag (so called "downgauging"). + Opportunity to reduce the reliance on fossil fuels through the use of bioplastics (attractive in times of rising oil prices) – An investment in time and money is required to replace a relatively small volume of plastic in comparison with general use of medical grade PVC
Compatibility	+ Existing knowledge regarding polymerization is still relevant

	+ The adaption of waste management flows should not be required where the practice of incineration is continued + Compatible with industry efforts to demonstrate eco- credentials in the face of concerns over growing waste, emissions and global warming – New technology required for production processes – There may be a compatibility issue with existing equipment used by the customers and with supplementary devices (e.g. tubing connected to the bags) – New supplier relationships may be required with feedstock producers
Complexity	– Blood bags are a complex product controlled by a strict regulatory environment. – The regulatory environment is not globally harmonised – If new blends and/or environmentally friendly additives are required there may be a significant R&D timeframe and corresponding expenditure – Testing costs and complexity will be high to meet with global medical standards – Training required for production staff where new blends/softeners are used – New supply chains and logistics arrangements may be required
Trialability	+ Producing medical grade plastics from third party resins could potentially allow smaller manufacturers to get a foothold on the market while building their supply chain without a significant upfront investment in R&D – Trialability is low due to the upfront investment required by the industry in R&D, technology and marketing. This increases the risk for smaller players. – The lead time for introducing an approved product to market is long (5-10 years) due to testing and approval requirements
Observability	+ Clear growing market for non-PVC in medical products
Risk	– Uncertainty regarding market potential – Uncertainty regarding legislative developments – Admitting liability for current product failings could lead to future litigation – Cannibalisation of existing market

6 Barriers

Blood bags are a complex product. Considerations when developing a new solution include functionality, environmental performance, quality, patient safety, handling, user friendliness and compatibility with other equipment.

In order to stimulate the development of a substitute it is important to recognise the barriers which exist in order that the ultimate strategy can work towards overcoming those which block the stated objective.

There are four primary barriers which need to be addressed in order to promote the development of a substitute product:

(1) Political, Institutional and Legislative

(2) Financial

(3) Market Economics

(4) Technical

Factors Determining the Rate of Innovation & Diffusion	***Current Barriers***
Political, Institutional and Legislative	• Lack of globally harmonised legislation • Environmental pressures vary considerably according to the industry and geographical location of a firm's activity • Lack of knowledge of PVC lifecycle hazards, hospital use of PVC and the availability of PVC-free products • The “grandfathering” of older medical products • Existing buyer contracts and procurement processes
Financial	• Commitment to significant upfront investment by manufacturers • Lack of investment capacity for R&D and capacity building by niche players • Costs of transition and often higher cost of PVC substitutes to end users
Market Economics	• A DEHP-PVC replacement programme requires action by the whole supply chain • The vested interests of traditional plastics producers and path dependency • Low crude oil prices making non-fossil alternatives potentially less competitive • Lack of clear demand • Limited number of PVC-free vendors
Technical	• Currently there is no technical solution which offers the performance of DEHP-PVC • Requires a long lead time as well as significant investment in R&D and testing to bring a new product to market

	• Low production capacity resulting in high unit costs • Changes will be required to non-bag components (i.e. tubing) as well as supporting infrastructure (e.g. storage systems) • Potentially requires changes to waste treatment systems

The main barrier today is a technical one. However, solving this requires manufacturers to be motivated through a clear and attractive customer demand or alternatively legislation. Different sized manufacturers will face different economic challenges with the smallest lacking the resources to take the risk and the largest needing a clear incentive to change from the status quo.

7 Conclusions

Blood bags represent a niche product for PVC with small volumes relative to other uses. The supply chain is dominated by a small number of specialised producers, generally wielding significant market power. These companies have integrated global operations and have invested significant sums of money in their current production capabilities leading to path dependency. Furthermore, the economics from a manufacturer perspective have shown a general decline in recent years with greater investment now going towards automated devices.

There is also a non-harmonised regulatory environment, making the investment in a replacement bag more costly and difficult to justify for manufacturers. Overcoming these barriers requires legislation and/or concerted pressure from buyers at a level whereby the market size is clear and attractive. This means demonstrating a clear European/Global demand, although Sweden could act as a lead/reference customer.

On a positive note, research has shown that buyer led initiatives have been successful in bringing forward PVC alternatives for nearly all other medical devices. Furthermore, the cost of these products is on par with PVC versions in most cases. On the downside, the lack of success with bringing forward an alternative to red blood cells seems to have most to do with the role of DEHP in stabilising red blood cells combined with the overall performance and low cost of PVC. This is real technical challenge to be overcome by manufacturers in addition to the general economic, legislative and institutional barriers. Recent efforts have revolved around finding alternative softeners to DEHP which offer these preservative qualities, while still retaining PVC as the polymer. Eastman Chemicals and BASF both now offer alternatives to DEHP, thereby providing a clear alternative without altering other aspects of their PVC manufacturing value chain.

The economic analysis performed as part of the current project demonstrates that it is economically feasible to manufacture the prototype polyolefin blood bag at a price very close to today's PVC blood bags. Furthermore, the time to market and the breakeven period for the upfront investment are both relatively short.

The primary economic risk to those companies involved in the current project, aside from the technical risks of manufacturing a new product, is that they fail to generate adequate demand due to

the higher cost at low production volumes. To overcome this risk one option is to loss lead, whereby the manufacturer initially sells at a loss in order to stimulate demand, thereby bringing down the production costs through economies of scale. Another alternative, is to differentiate the new bag based on its health benefits and initially target the high-risk patient segments. Engagement with those responsible for procuring blood bags will help to determine whether they are prepared to pay a higher price per bag for a small volume, on health and environmental grounds, and therefore a small annual increase in cost.

A further risk stems from the current incumbents. Although they are currently pursuing a strategy of replacing DEHP with alternative softeners, they may themselves develop and market a non-PVC bag if a clear market is seen to exist, or alternatively reduce the price of their existing PVC products to protect market share. The companies involved in the existing project should seek to mitigate this risk by negotiating longer term contracts with buyers in order to lock in demand prior to making any upfront investments.

From the buyer perspective, this feasibility study has demonstrated that it is possible to procure a substitute bag at a competitive market price, particularly where upfront, longer term commitments are made. Although Karolinska University Hospital alone is not large enough to stimulate the market, a group of 10-20 similar hospitals across Europe could be enough to kick-start the market. A technology procurement project co-ordinated across a group of like-minded hospitals would seem to be a feasible procurement strategy.

In summary, despite a number of outstanding technical challenges, the economic analysis performed in this study suggests that, with co-ordinated and motivated set of buyers, the prototype developed in the project is economically viable and attractive to those companies participating in the project. Furthermore, if a clear demand is demonstrated, the global healthcare companies that dominate the PVC blood bag market could similarly produce a non-PVC blood bag at a price almost identical to that of today's PVC bags.

8 Appendix - Financial Model

The attached financial model has been used to underpin the economic feasibility study contained in the attached report.

Life+ Financial Model v1.0.xlsx