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Manufacture of Bovine Serum Albumin

Serum albumin is a protein that occurs in small quantities in the plasma phase of animal blood. Concentrations in whole blood are approximately 1.3% with an average recoverable yield from plasma of 2%. Serum albumin has a wide range of commercial uses depending on the grade, purity and quality of the product. Current users in Australia include the following market sectors:

- diagnostics
- pharmaceuticals, biologicals and vaccines
- agricultural biotechnology
- animal breeding
- marine biotechnology and aquaculture
- food and beverages
- chemicals and enzymes
- hospitals and research institutions.

Over 80 users of serum albumin have been identified in Australia and New Zealand, excluding hospitals and research institutions.

The serum albumin market is already well established with standard catalogue entries for beef, sheep, goat, horse, chicken, hamster, donkey and pig albumin in most major biochemical supply houses' retail lists. For scientific applications (where it has predominantly been used in diagnostic tests) bovine serum albumin has traditionally been the albumin of choice. The availability of bovine albumin, due to the ease of collection of bovine plasma, has probably assured its widespread availability and use.

The emergence of BSE has, however, created an increased market opportunity for albumin from other species. Porcine albumin is not well accepted due to religious objections from some markets. Ovine albumin presents good opportunities despite lower yields and some historical difficulties in collecting ovine blood without haemolysis and extraneous contamination. Modern techniques of albumin

extraction allow for the extraction of albumin from haemolysed blood as well as from high-quality plasma. Consequently there are currently no identified technical objections to manufacturing sheep albumin. The Australian sheep market is free of scrapie infection, which will provide an additional market opportunity for all ovine products including ovine serum albumin.

Blood albumin does not have a monopoly on the albumin market with its major competitor being, in some applications, milk protein. The cloning of the albumin gene may, in future, allow for recombinant techniques to produce albumin that will take a significant share of the market away from animal-sourced albumins.

Bovine albumin grades and possible values

The following grades of bovine albumin have identified uses and markets.

- Reagent grade BSA—used in scientific applications outside the therapeutic and veterinary field.
- IgG-free BSA—used for immuno assays that may be subject to interference by bovine gammaglobulins, as a serology diluent and as an enzyme-system stabiliser.
- IgG, Fatty-acid-free BSA—used as a cell-culture medium, for immuno assays, as an enzyme diluent in diagnostics, as a serological diluent and as a general protein stabiliser. Preparation is from concentrated reagent-grade BSA with IgG and Fatty acid removed by solvent extraction.
- IgG, Fatty acid, Endotoxin-free BSA—used as a cell-culture medium, an ELIZA blocking agent, as an enzyme or serology diluent, as a protein stabiliser and as a carrier protein. It is prepared from reagent-grade BSA treated to remove endotoxin, IgG and Fatty acid.

Note. While designated as 'free' of IgG, Fatty acid and endotoxin, these grades are in fact 'low level' with levels of these specific components reduced to below an acceptable level.



The costs to produce, and prices received for, these products depend on the level of purity, extent of further processing required and yields obtained. Indicative prices for the different grades range from \$4,000 to \$50,000 per kilogram.

Production of albumin

Albumin can be recovered by a number of different techniques including ion-exchange chromatography, salt fractionation, selective denaturation and pH titration. Large-scale production requires:

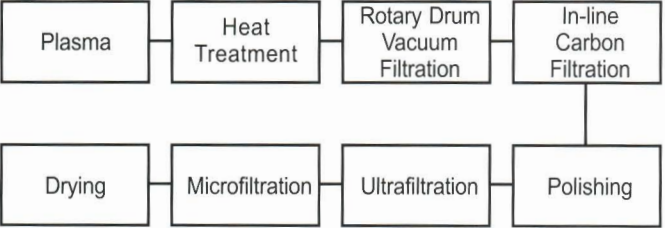
- simple methodology;
- readily available plant and equipment;
- a good source of raw material;
- qualified staff.

Selective denaturation techniques are the most likely application for Australian meat industry partners. They are the most attractive option because they are:

- simple, minimum-step methods that provide a good yield of product (20 kg per tonne of plasma);
- capable of producing product with protein purity that is generally high (>98%);
- suitable for recovery of albumin from bovine, ovine and porcine plasma;
- techniques requiring 'off-the-shelf' filtration equipment, drawing on the same equipment suppliers as the food industry and, in particular, the wine industry.

The process flow is outlined in Figure 1.

Figure 1. Selective denaturation of plasma to extract albumin



The food and wine industries commonly use the type of equipment required for vacuum filtering and ultrafiltration. Proprietary activated carbon filters and micro-filters, which are used in the brewing industry, are ideal for polishing the albumin solution.

Drying of the product is generally by freeze drying although spray drying may also be used. Services are available in Australia for contract freeze drying and spray drying; however dependence on contract drying services may create a weak link in the production process as the highest standards are required to produce sterile product. Commercial freeze driers are manufactured in Australia (eg Oriel manufacturing) so that a suitable drier could be included at the processing site.

Estimated capital costs (1995 estimates + 2% CPI), not including drying equipment, for a batch process handling

3,000 – 5,000 litres of plasma per triple shift have been determined as follows.

200 sq metre building & fittings	\$433,000
Rotary drum vacuum filter	\$86,000
Flow-through filters	\$13,000
Ultrafiltration	\$65,000
Plumbing, tanks, services, CIP	\$49,000
Total	\$646,000

As the selective-denaturation technique for albumin recovery includes a heat-treatment step, it is logical to site the process at the plasma collection point to eliminate the need to chill the plasma for transportation to the processing site. As it may be difficult to match multi-shift albumin production to a single blood-collection shift, it may be impossible to totally eliminate plasma chilling. Costs for chilling and reheating plasma can be minimised with careful planning and equipment sizing.

The preliminary costing above has been prepared on a batch process. The process can, however, operate on a continuous basis which would be expected to realise some economies related to reduced processing time and reduced energy consumption.

Plasma production should be established at a level to achieve economy of scale. This would enable the provision of plasma to the process at a competitive price. This may be achieved with a plant dedicated to high-volume production of plasma for the edible-food market. As identified in the MLA Co-products brochure *Potential uses of blood products* many food producers in Australia are currently reluctant to use plasma products in food because of the perceived reaction of consumers to blood products and the ambiguous labelling situation throughout the food industry.

The raw material for the albumin process need not be the best quality plasma—based on the level of haemoglobin present. This process can tolerate plasma with high amounts of haemoglobin; however, the plasma needs to be screened for virus content as well as the final product. This can be done by the Department of Primary Industries Animal Research Institute in Brisbane.

This process is a higher technology process than those normally encountered on an abattoir site. Consequently it will need to be under the supervision of a person having knowledge of the required processes and standards to be achieved. It would be expected that the person would hold a science degree, or equivalent, and preferably have experience in the processing of fine chemicals or pharmaceutical products.

Plasma costs

This process is reliant on a stable and economic supply of plasma. Estimated costs have been prepared for the construction and fitting of a facility for the collection of edible blood and its separation to plasma and cell fraction at an abattoir in Australia. Costs are estimated for an abattoir with slaughter capacity of 525 head of cattle on a single shift and 825 head over two shifts and are given in Table 1.

Table 1. Estimated costs for facility to produce plasma on an abattoir site (1996 figures + 2% pa CPI)

Item	Budget cost
Building construction/alterations	\$102,000
Blood collection equipment	\$127,000
Blood separation equipment	\$105,000
Laboratory	\$11,000
Miscellaneous	\$30,000
Total	\$375,000

The profitability of the plant is dependent on the blood throughput. Preliminary cost analysis has indicated that, for a range of throughputs, the cost of production, break-even selling price for plasma, and payback period for the plant is likely to be as given in Table 2. These estimates are based on recovery of 8 litres of blood per head of cattle.

Table 2. Estimated returns for blood separation to plasma and cell fraction. (1996 figures)

Slaughter per day	No. of shifts	Production cost per kg plasma	Break-even plasma sell price per litre	Payback period
525	1	\$0.94	\$1.40	15 months
750	2	\$0.93	\$1.25	10 months
825	2	\$0.89	\$1.20	9 months

It is essential that all costs and prices be confirmed as part of a cost/benefit analysis prior to considering investment in new technology.

It is important, when considering an investment in this technology, to recognise that the serum albumin is only a small part of the plasma raw material and that other plasma components can be co-produced with the serum albumin. Any cost/benefit analysis should consider the cost and return from any co-products produced.

Further reading

This information is a summary of information from the following project funded by the Meat Research Corporation.

Project UGR.002: Value Added Proteins and Enzyme Recovery from the Meat Industry

Further detail is available from the final project report for this project and the project paper 'Estimates of the Cost of Manufacture of Bovine Serum Albumin'—both of which are available from Meat and Livestock Australia.

Related information is given in these MLA Co-products brochures.

- Potential Uses of Blood Products
- Edible Collection of Blood
- Separation and Stabilisation of Useable Blood Components
- Recovery of specific proteins and enzymes from blood: Part 1 – Aprotinin, transglutaminase, fibronectin and related proteins
- Recovery of specific proteins and enzymes from blood: Part 2 – Growth factors

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