NATIONAL BLOOD SERVICE

SAFER PLASMA IN COMPONENTS (SPIC)

Phase 1: Evaluation and Feasibility Study
Stage 1: Frozen Plasma Components

Section 4: Methylene Blue Feasibility and Pilot Study

SAFER PLASMA IN COMPONENTS

Feasibility Study on the Implementation of a Process for the Methylene Blue Viral Inactivation of Fresh Frozen Plasma

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1. Aims and objectives of the project

The aim of this feasibility study is to carry out scientific and operational assessment of a Methylene Blue (MB) viral inactivation system for the treatment of therapeutic Fresh Frozen Plasma currently produced by the NBS, either in total or plasma for specific uses, and distributed to user hospitals.

The system chosen for evaluation is a combination of the Macopharma MB treatment process and MB removal using the Pall removal filter.

The Macopharma MB viral inactivation process is an in-house procedure using technology developed by Springe (Red Cross centre of Lower Saxony/Springe, Germany). It is a proprietary patented procedure for inactivation of enveloped viruses in fresh frozen plasma using visible light in the presence of 1 μM Methylene Blue. The procedure is based on passing filtered plasma over a MB pellet into a plasma storage pack, with the subsequent exposure of the plasma plus MB to light at a wavelength of 590 nm in the 'Maco-tronic' illumination system.

The second phase involves the sterile docking of the treated plasma to a Pall MB removal filter, and the filtration of the plasma into final integral plasma storage pack.

The objectives of the study are to assess the following;

- the effect of methylene blue treatment and removal on the quality of the resultant plasma component under routine operational conditions, i.e. conformance to UKBTS (Red Book) component specification.
- the procedures in routine operational use for compliance with the requirements of GMP, and the general suitability of the system for use by the NBS.
- the operational impact of the MB system on the NBS, in terms of space, staff, and equipment based on implementation of viral inactivation at levels of between 10% and 100% of current FFP production, including both adult and neonatal components.
- the options for provision of other plasma components in a viral inactivated form.
- the user acceptability of the final component.
- the potential hospital demand for a methylene blue FFP component, with and without MB removal.

2. Design of the Operational Evaluation

The objective of the evaluation process is to demonstrate that the Macopharma MB system with MB removal is suitable for the production and storage of virally inactivated products to the standard given in the current edition of the Guidelines for the Blood Transfusion Services of the United Kingdom (referred to as UKBTS Guidelines) under routine operational conditions. It is important to note that the current edition of the guidelines (4th edition) does not include a methylene blue removal step.

The evaluation consists of three main phases termed 0,1 and 2.

Phase 0 Scientific Evaluation

The purpose of the phase 0 evaluation is to determine in a limited number of plasma units in vitro whether the MB system is expected to have any affect on plasma which may effect its clinical efficacy or safety.
The framework for the evaluation is provided by the UKBTS Guidelines, Chapter 7, Generic Evaluation Protocols. The investigation consisted of three main elements: an assessment of data supplied by the manufacturer, an assessment of the data provided by SNBTS (phase 0), and data from actual testing carried out by the NBS (Components Development Laboratory). Full details, including signed copies of phase 0 evaluation reports, or copies of data provided by manufacturers in lieu of these are held with the SPIC project board document register.

Phase 1 Operational Evaluation

This is an initial evaluation of the process in a working processing environment. It is carried out on two NBS sites and comprises the full processing of 125 donations. This allows for the assessment of materials, equipment and processes, and following the manufacturer's recommended use of the system, the completion of standard operating procedures for the next phase of the evaluation.
Components produced during this phase are not released for therapeutic use. They are subject to 100% testing for quality parameters (as per UKBTS Component Guideline Specification). The quality monitoring data provided is used to determine the capability of the system and to give some indication on the frequency of quality monitoring required for phase 2.

Phase 2 Operational Evaluation

Phase 2 involves a more extensive use of the system under full operational conditions, so that expected (routine) processing volumes for virally inactivated plasma will be achieved within the processing departments. This aspect is more important than processing absolute numbers of packs as it provides significant information on the capability of the process and an understanding of the potential impact of implementing such a process. For

the trial the volume was set at 30% of normal FFP processing volumes over a period of two weeks.

Components produced during phase 2 are available for therapeutic use, however, this was restricted to a limited number of hospitals collaborating with the NBS on this work.

The Protocol for the Operational Evaluation of the Macopharma Methylene Blue Inactivation System combined with the Pall Methylene Blue Removal System are held with the SPIC project board document register.

Criteria examined during Operational Evaluation

1. Machine safety and operation

Includes electrical safety testing (PAT) of the equipment, an examination of the machine for any point of potential harm to the product or the operator, and an assessment of the suitability of the environmental conditions (as defined by the supplier).

Evidence of planned maintenance schedules, either provided by the supplier, or routine operator maintenance.

Confirmation of arrangements for technical support and availability of spare parts for the equipment.

2. Consumables, availability, storage conditions and shelf-life

Determination of the storage requirements for MB consumables and that these can be met, and that the shelf-life of the consumables is sufficient to meet the needs of the NBS.

3. Instructions for use

Confirmation that the instructions for use of the equipment and packs are provided, that these are sufficiently detailed, closely define the constraints under which the system can be operated and that these can be met under the current conditions for preparation of blood components in NBS facilities. Assurance that the suppliers can provide training for NBS staff in the operation of the equipment and the MB process, and that they can provide sufficient ongoing support in a timely manner during the evaluation period.

4. Regulatory approval for the system

Confirmation that the consumables and equipment are CE marked and that certificated evidence from a regulatory body is provided.

5. Equipment calibration

That the supplier can provide evidence of calibration (where appropriate) of

control systems within the illuminator system e.g. for light exposure, temperature control, and timing control.

6. Pack and Label suitability

Determination of the suitability of pack label, that it complies with UK requirements, that additional overstick labels can be securely applied, and that all barcode information is in the correct format and can be read and recorded by NBS systems.

Confirmation that the final plasma storage pack complies to NBS blood pack specification, and an assessment of faults which may relate to manufacturing defects or process related. The packs must be assessed for user acceptability (appearance, compatibility of administration ports etc.).

Assurance that sterile connection can be achieved safely and securely between the MB system and pack systems from a variety of other suppliers, that the tubing is of adequate length and resilience, and compatible with heat sealing devices in current use within the NBS.

7. Filter (leucodepletion and MB removal) effectiveness

Confirmation that both the filters are effective in their action, and that they are not subject to blockage.

8. Machine suitability

An assessment of the suitability of the MB illumination device for routine use in terms of:

Indication of partial exposure
Lid lock to prevent interference during exposure cycle
Indication of cycle completion
Suitability of warning alarms and error messages
Machine reliability

9. Product suitability

Confirmation that the MB component produced complies with UKBTS Component Guidelines, and that it is compatible with current packaging and storage systems in current use within the NBS and user hospitals.

10. Health and safety issues

An assessment of any Health and Safety issues which may arise from the use this pack system and associated equipment which may have a detrimental impact on staff.

The Protocol for the Operational Evaluation of the Macopharma Methylene Blue Inactivation System combined with the Pall Methylene Blue Removal System are held with the SPIC project board document register.

3. Regulatory and Quality Aspects

3.1 Licensing Issues

Methylene blue-treated FFP (MB FFP) is a different type of product from that which the NBS has supplied to hospitals in the past. Previously, blood components supplied by the NBS have only had added to them the anticoagulant and storage-enhancing solutions necessary for their production. The addition of an active ingredient is new and different and the exact details of the regulatory implications are still not known. For this reason, some background information is given below on the current arrangements for the supply of existing blood components by the NBS as well as for the commercial MB FFP which has reached the market by a different route from that used by the NBS.

The NBS provides unlicensed medicinal products for human use to UK hospitals. These products are commonly known as "Specials". This category of product is unique to the UK. The Medicines Control Agency regulates medicinal products for human use on behalf of the Licensing Authority in accordance with the Medicines for Human Use (Marketing Authorisations etc) Regulations 1994 and the Medicines Act 1968. The placing on the market of products which do not have a marketing authorisation or a product licence is done under strictly controlled conditions, since unlike licensed products the unlicensed products have not been assessed by the Licensing Authority for safety, quality and efficacy. For the current components supplied by the NBS, these controls have been developed over a number of years and are based on GMP requirements and guidelines such as the Guidelines for the Blood Transfusion Services (Red Book).

The products which the NBS is authorised to manufacture and assemble are described in our licence application. Therefore the MCA has been informed by letter on 29 August that trials were to begin of VIP made from the Macopharma process, equipment and consumables. So far, we have had no requests for further information by the MCA. As part of the introduction into routine use of MB FFP, we would apply for a variation to our licence and details of our controls for this product may be requested at this time. The work done during the evaluations will help in this respect.

By contrast, the commercial product, Octoplas, was licensed by the MCA in March 1998 for five years (Product Licence Number 10673/009) to be placed on the UK market. Octoplas is a pooled product which is made from Austrian/German plasma. In order to obtain this licence Octopharma would have had to supply the MCA with extensive data on the clinical trials carried out and other data to make up the drug master file. The NBS's product would be put on the market in a different way, as described above.

3.2 Macopharma VIP Process and Equipment

The Macopharma VIP pack and associated equipment have been classed as a medical device. This means that they are covered by the same arrangements which apply to existing blood packs, as defined by the Medical Devices Directive (93/42/EEC), which has been put into UK law. The regulations allow the approval of a product by a Notified body in any EU county and the subsequent marketing in all EU countries. The Macopharma VIP packs and the equipment which is needed to illuminate the packs have been classified as a IIb device, which is the next to highest risk category. This puts it in the same category as blood packs (without an active ingredient). The device can be placed on the market through a number of routes through the approval process. The two basic routes are through a full assessment of the supplier's quality system or by a type examination of the product followed by product verification or audit.

The approval for the Macopharma system was granted by TUV Product Service of Munich on 02 February 2000. The Certificate is for "Devices and equipment for the leucodepletion and the viral inactivation of plasma by the technique of phototreatment with methylene blue". The certificate is valid until 04 February 2001. The approval is by the route which involves a quality system audit by a Notified body to the EN 46001 standard. This route to CE marking does not require the Notified body to examine the equipment before it can be put on the market. An important point for the evaluation of a device such as this by a user, such as the NBS, is that there are few technical requirements that are relevant apart from the basic blood pack part of the system. Our evaluation must therefore be extensive.

Macopharma are dependent on two key suppliers to them, one for the MB pellets and one for the manufacture of the equipment for illumination of the packs. It is believed that the MB pellet which is put into the pack assembly is supplied by the University of Lille. This will be established at audit. The manufacture of the light boxes is carried out by a company called Vilbert Lourmat.

3.3 Supply of Hardware and Consumables

Introduction of the Macopharma MB system would mean that the NBS was completely reliant on one company for the supply of consumables and support for the maintenance and repair of the associated equipment. The track record of Macopharma since the NBS has been using its packs is mixed. Initially there were difficulties with labels and there have been others since.

Experience with supply of blood packs over a number of years indicates that all suppliers of packs are subject to manufacturing defects in their products. This sometimes causes, after discussions with suppliers, to precautionary withdrawal of a batch of packs and for this reason it is necessary for supplies of packs from different batches to be available. This point is particularly relevant since there will be only one supplier in this case.

In line with NBS procedures, an appraisal of the quality systems in use by the supplier will be carried out through an on-site audit of a number of relevant activities. This audit is scheduled for the 21 November 2000.

The NBS will also depend on a small number of MB illumination machines for its production capacity and therefore from a quality point of view, a detailed contract for the support of these illumination machines is required. Possibly a spare, back-up machine will be required.

4. GMP Requirements

4.1 System-specific GMP and Quality Issues

The design and operation of the system presents a number of issues in relation to GMP. The main ones are listed below.

- the secure transfer of the donation number between the collection pack, the MB pack and the final presentation pack;
- the correct addition of an appropriate amount of MB for the amount of plasma which is to be inactivated;
- monitoring that each pack has received the correct amount of light to expose the FPP plus MB so as to complete the inactivation process;
- a means of positively identifying that each pack has been exposed;
- suitability of the final presentation pack for freezing and storage and supply to hospitals without breakage.

The ability of the system in relation to these issues will be established during the evaluations.

4.2 Non-specific GMP and Quality Issues

In addition to the specific issues above, there are a number of more general issues which are listed below.

- provision of technical specifications and operating information for the system and the consumables;
- calibration of various features and functions of the equipment;
- provision of suitable maintenance for equipment;
- final pack base label suitability and its ability to adhere blood group and other labels added by the NBS;
- provision of alarms and warnings in the event of a failure to complete

correct exposure cycle.

As above, the ability of the system in relation to these issues will be established during the evaluations.

5. Phase 0, 1 and 2 Evaluations

A detailed account of the evaluations is given later in this report. The principles of the evaluations are that in Phase 0 the product must be found to meet existing product specifications in the Red Book as well as pass other tests indicating clinical suitability. In Phase 1 the equipment and the consumables must be proved to meet Quality and GMP requirements as well as produce a product that meets Red Book product specifications and be operationally suitable. Phase 2 is an extension of Phase 1 to confirm that in larger scale use the same requirements as at Phase 1 are met.

6. Process Control and Monitoring

The existing arrangements for process control and monitoring of blood components such as FFP are based on statistical methods for monitoring the levels of white cell contamination and on post-production sampling for other characteristics. The monitoring of MB FPP will be based on a specification taken from the Red Book. In the fourth edition there is a specification for FFP, leucocyte depleted, MB treated which specifies four parameters which are to be monitored: the volume, the number of platelets, the Factor VIII levels and the leucocyte count.. A maximum level of MB after processing is given in the technical information. Statistical methods will be used to monitor the number of leucocytes. For the others parameters, samples will be taken and compared with the minimum pass rate.

7. Quality Plans

In accordance with the requirements of quality system standards, a Quality Plan is needed for the project. This can be developed as the project progresses and should cover the following headings.

Introduction and Project Objective
Personnel and Responsibilities
Applicable Standards
Quality Control Requirements
Documentation Requirements
Product Specifications and Testing
Validation
Release of Product
Pack and Labelling Requirements

The Quality Plan will complement the Project Initiation Document and the protocols for the evaluations.

4. Description of the Macopharma MB system with MB removal

Plasma from a single donation in a blood pack containing a phenothiazine dye methylene blue in a pellet form, is exposed to white light. The MB binds to guanine/cytosine base pairs, and on light exposure toxic oxygen radicals are generated which prevent replication of viral nucleic acid and also alter some core and envelope proteins.

After treatment the residual level of MB is less than 0.5 μg/ml. Although MB and its photoderivatives disappear rapidly from the circulation, with a half life measured in minutes, some concern has been raised over toxicity and it is possible to remove > 90% of residual MB by filtration.

The treatment is effective against small and large enveloped viruses with RNA or DNA genomes (4-6 log removal of HIV, HBV, HCV), but less effective against small non-enveloped RNA viruses, which include hepatitis A, there is also evidence that it may have some efficacy against selected non-lipid viruses, including parvovirus B19.

Overview of the system and components

The system under evaluation was to provide Methylene Blue (MB) treatment of individual units of fresh donor plasma with secondary removal of methylene blue and its breakdown products by further filtration.

In summary, the system requires the sterile connection of a methylene blue treatment pack (Macopharma) to a pack of freshly prepared donor plasma. The connecting tube between the two packs is bisected by a small chamber housing a pellet of methylene blue which dissolves as the plasma passes over it. The concentration of MB in the resultant plasma is approx. 320 μg/L (1μmole).

The plasma is transferred from the original donor pack into the methylene blue treatment pack and then placed inside a lightbox which exposes the pack to light of specific wavelength range (max 590nm). During the illumination procedure viral inactivation takes place. Following inactivation, residual methylene blue is removed by passing the treated plasma through a methylene blue removal filter (Pall Medsep). It should be noted that methylene blue treatment causes a loss of some coagulation factors and there is a lower specification for this product than for standard FFP. The treated plasma is then frozen and stored until required as for standard FFP.

Equipment

The illumination device (the Macotronic) is marketed by Macopharma and is designed specifically for the illumination of plasma in methylene blue treatment packs produced by Macopharma. Macopharma do not support the use of this machine with any other suppliers methylene blue treatment packs which means that we would have to accept a single supplier scenario for the use of the system under trial.

The Maco-tronic illumination system is a free standing device which is linked to and controlled by a PC. It incorporates a refrigeration system for the temperature control of the illumination tray. The device houses 6 sodium lamps (3 above and three below the tray), and the illumination tray agitates the plasma during the cycle.

A laser scanner, attached to the PC, enables donation and pack lot numbers to be scanned into the PC, creating a positive link with the donation. The illumination is controlled by the PC with each lamp being monitored independently.

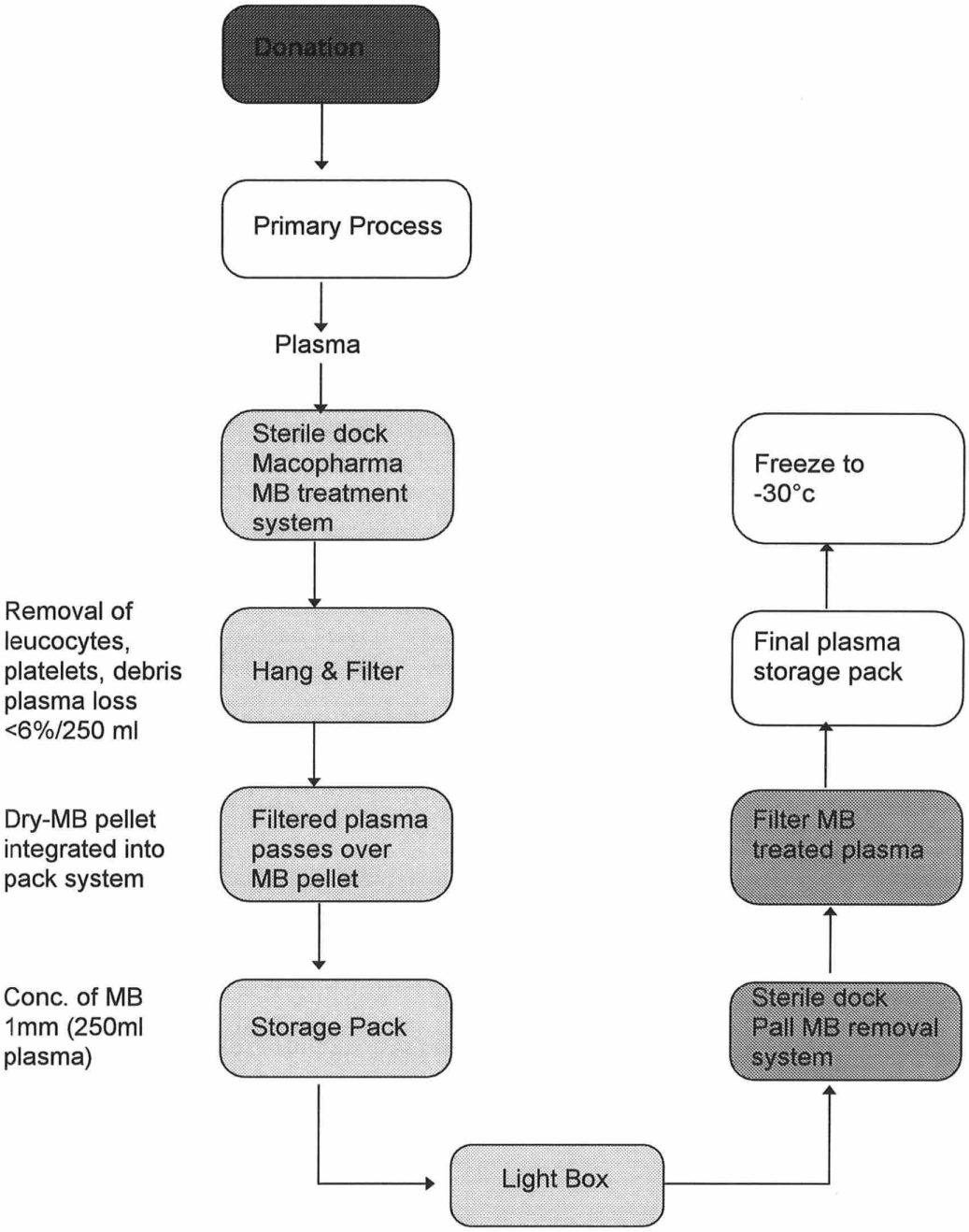
At the end of each cycle a printout is produced automatically which graphically illustrates the performance of each sodium tube and identifies the scanned donation and lot numbers of the pack, the total light energy emitted and the maximum temperature reached.

The Macotronic is a relatively large item of equipment (similar in size to a floor standing photocopier) and although large, the equipment is only designed for the treatment of a maximum of 3 packs of plasma during any one cycle, each illumination cycle taking approximately 25 minutes.

Consumables

The system under evaluation utilised methylene blue treatment packs from Macopharma and methylene blue removal filters from Pall Medsep.

Methylene Blue Viral Inactivation Process



- 6 sodium, low pressure high energy lamps.
- Emission maximum 590 mm.
- Illuminates 3 packs/cycle.
- Temperature controlled (20 ± 2°c).
- Fully PC controlled, fully documented process (time, individual lamp intensity, temperature etc).

5. Evaluation Summary

5.1 Phase 0 Evaluation of Macopharma Methylene Blue System

1. Macopharma Methylene Blue System

The purpose of these evaluations is to determine in a limited number of plasma units in vitro whether this system is expected to have any effect on plasma which may effect its clinical efficacy or safety. Since the Macopharma MB system comprises a leucodepletion step prior to MB treatment it is important to know the relative contributions of both processes to any effect on the final quality of plasma. For full details, signed copies of Phase 0 evaluation reports, or copies of data provided by manufacturers in lieu of these, are held with the SPIC project board document register.

1.1 Data provided by the manufacturer

Previous data provided by Macopharma on the filter used in the MB system to leucodeplete plasma (PLAS4) suggests that this filter has minimal effect on coagulation factor activity, coagulation activation or complement activation. This filter is currently used as an integral plasma filter as part of their BAT system. Data on this system supplied by Macopharma was accepted by the National Leucodepletion Science and Quality Group for the Phase 0 evaluation. Further data provided by Macopharma suggests that the MB system results in a 10-20% loss of coagulation factor activity. However, during the phase 1 evaluation of this system by the NBS it transpired that the data provided by Macopharma was using a system with a different light source and illumination time than that offered to the NBS.

1.2 Data provided by the Scottish National Blood Transfusion Service (SNBTS)

Evaluation data was provided from the SNBTS using the Macopharma MB system offered to the NBS. There was a reported loss of coagulation factor activity of 10-30%, which was most noticeable for FVIII and fibrinogen. The loss of coagulation factor activity was deemed clinically acceptable. The results on coagulation and complement activation markers were deemed inadequate by the NBS since these were only examined post-leucodepletion and not post MB treatment. Data from SNBTS was accepted as the phase 0 evaluation for plasma treated with the Macopharma MB system provided final levels of activation markers in plasma were studied as part of the MB removal filter evaluation.

2. Pall Methylene Blue Removal System

2.1 Data from manufacturer

Data provided by the manufacturer was inadequate to replace a phase 0 evaluation on this product and some work was also required due to

deficiencies in the evaluation data provided by Scotland for the MB system itself. A full phase 0 evaluation was performed by the NBS. In addition to taking samples pre and post-removal filter, samples were also taken pre and post addition of MB to plasma as there was concern that MB may interfere in the assay systems used.

2.2 Data from NBS Phase 0 evaluation

Data from the NBS evaluation showed that there was a loss of 10-40% of coagulation factor activity due to MB treatment of plasma. This was most noticeable for Factor VIII and fibrinogen, where levels were decreased by approximately 40%. The removal filter appeared to have minimal effect on any parameters studied, but due to a possible effect of MB on the assay systems a small effect on APTT based coagulation factors cannot be excluded (probably FVIII and FXI). There was no gross activation of complement or coagulation. Although there was a decrease in coagulation factor activity due to MB treatment, with the exception of fibrinogen, the level of all coagulation factors studied remained within normal ranges for plasma. However, for fibrinogen, levels in the final product were below normal. The residual levels of coagulation factor activity were deemed clinically acceptable. Samples were sent for independent testing by experts in the field with alternative assays for fibrinogen. This revealed that the MB treatment did not effect the absolute concentration of fibrinogen, but appeared to have an effect on fibrin polymerisation. The clinical significance of this is unclear without further investigation.

3. Recommendations from the phase 0 evaluations

Since there is considerable loss of coagulation factor activity due to MB treatment the choice of starting plasma is important as we do not want to compound these losses further. Filters used to leucodeplete are known to have differential effects on coagulation factor removal. Therefore preferentially only non-leucodepleted plasma should be used as a start product. If this is not possible, then plasma must be obtained by filtration with a filter which has been demonstrated to have minimal effect on plasma quality. Currently, the Baxter R7490, previously evaluated by the NBS, would fulfil this criteria.

Since fibrinogen levels appear to be effected by MB treatment and may be dependent upon the assay used to measure them, the production of cryoprecipitate from MB plasma should be evaluated further since quality monitoring of fibrinogen may prove problematical.

It was not possible to outsource measurement of residual MB in units. If this is deemed necessary for routine quality monitoring this will have to be investigated further.

5.2 Operational summary - Phases 1 and 2

Leeds and Birmingham centres were chosen for the operational evaluations and a single Maco-tronic illumination machine was sited in each processing department. Following set up and familiarisation during phase 1 packs were processed over a 2 week period at 30% of total FFP production, the packs were treated on the evening of day 0 (day of donation) and prior to freezing.

Dosing of plasma with methylene blue:

The MB treatment pack is suitable for the treatment of plasma in the range 235 - 315 ml. This is based upon the quantity of active methylene blue contained in the pellet housed in the treatment pack. This range of plasma volumes does not complement the current range for standard fresh frozen plasma components manufactured by the NBS, this is extremely variable between blood centres and is dependant on the source material and specific hospital requirements (150 - 340 ml). It was necessary therefore to specifically select the units of plasma for MB treatment on a volume basis.

Prior to the evaluation it was noted that the manufacturers specification sheet was incorrect and two subsequent iterations of the specification sheet were also noted to have incorrect information. The information provided also conflicted with the information printed on the base label of the pack which stated that the packs were suitable for the treatment of 250 $\pm$ 50 ml of plasma. Macopharma were informed of the problem and agreed that the wrong labels (an earlier version) had been applied and that this would be corrected in subsequent batches. This was a minor but fairly fundamental matter that should have been resolved before this product was offered for sale and raises some concerns over the manufacturers' quality system.

To summarise this matter however, if the NBS intends to move forward with this system into routine use, it will be necessary to decide how we will deal with the issue of the volume range. This will largely depend on the percentage of plasma units we intend to treat with methylene blue. At a relatively small percentage, possibly up to 20%, we may be able to select units of a suitable volume for MB treatment whilst retaining the remaining units for standard FFP production. At higher percentages however such a policy may lead to increasing levels of wastage and it will be necessary either to amend our product specification and processes or to ensure the manufacturer alters the specification of the methylene blue treatment pack to meet our requirements. It does present an opportunity for the NBS to standardise nationally on FFP production processes.

The transfer of plasma from the original donor pack is a simple procedure but suffered from problems of solubility of the methylene blue pellet which on numerous occasions (80%) fell through into the receiving pack having only partially dissolved. In approximately 4% of packs the pellet lodged in the chamber and required manipulation to move the pellet into the treatment pack and further manipulation to fully dissolve the pellet. On a few occasions the pellet blocked the outlet port of the chamber, preventing plasma flow and further reducing the likelihood that the pellet would

dissolve. These specific episodes resulted in the loss of the product being treated.

The solubility problems and requirement to manually mix the plasma to ensure the pellet is fully dissolved is of concern and would be a major drawback if the procedure was to be used at high throughput where failure to notice an undissolved pellet is more likely and could potentially lead to an ineffective viral inactivation. This is a significant weakness in the system and indicates the high level of monitoring of the process required by operators.

Illumination of plasma

Packs dosed with methylene blue are then immediately transferred to the Macotronic for light treatment. The system as evaluated requires that pack donation numbers are scanned into the machine PC prior to treatment, the numbers entered are printed on a report at the end of the cycle. The system also incorporates a lid-locking mechanism to prevent packs being removed mid-cycle.

Despite this there are GMP concerns that the system provides no guarantee of exposure since there are currently no indicator labels to prove exposure (as there are for gamma irradiation) nor any colour change in the methylene blue following illumination, indeed there is no proof that the packs have been through the illumination cycle. Indicator labels have been evaluated previously, and although a significant colour change can be effected the change is due to exposure to light and therefore the indicator labels would have to kept in the correct guaranteed conditions (total darkness) prior to use. Improvement in this aspect of the procedure have been requested and discussions are ongoing. At the present time however, strict procedural control is required to ensure that packs fully complete each cycle, again another aspect requiring extreme vigilance and caution from the operators, with strict adherence to written protocols.

It was found that the throughput of the Macotronic was not as great as we had been led to believe and was nearer to 7 per hour rather than 9 as originally quoted. This is a considerable reduction in anticipated processing capacity. The procedure was relatively simple to carry out, consisting of a number of basic activities which were well within the capabilities of the processing staff.

The staff found that when working at full capacity with a single machine it was difficult to produce more that 30 - 40 units of treated plasma each evening because of the logistics of blood collection sessions, shift patterns within laboratories and more importantly the timescales over which we are currently required to complete plasma processing. There are two main issues; firstly, the in-house MB system has not been evaluated using plasma frozen and thawed prior to treatment, secondly, the NBS has not, at this time, evaluated the effect of extended hold prior to processing on standard FFP components.

Methylene Blue Removal

Following completion of the illumination cycle the lid lock is released and packs can be removed from the Macotronic for subsequent methylene blue removal. This is achieved by sterile connection to a Pall Medsep methylene blue removal pack into which the MB treated plasma is drained. This final storage pack is the same as a pack currently in use by the NBS for FFP storage and therefore poses no additional or unknown risks.

6. Health and Safety Aspects

HEALTH & SAFETY ASSESSMENT

FUNCTION: PTI

SITE: Birmingham

DESCRIPTION OF WORK AREA OR ACTIVITY: Methylene Blue viral inactivation of Plasma

HAZARDS IDENTIFIED	PERSONS AFFECTED	EXISTING CONTROL MEASURES	LIKELIHOOD (1-5)	SEVERITY (1-5)	RISK RATING	ADDITIONAL CONTROL MEASURES
Lifting and Handling Lid to Matronic illumination machine is hydraulic but hydraulics do not operate for the first 15cm/40° when opening or closing Without this hydraulic facility the lid is heavy and difficult to use.	All staff involved in the process	Hydraulics fitted but do not work for part of the manoeuvre	3	3	Medium	Request that Macro Pharma make adjustments to the Hydraulics on the lid
Trapping If the lid bangs shut it could cause a trapping hazard for fingers.	As above	Handle position designed on top of the lid to avoid operators trapping hands	2/3	3	Medium	As above
Equipment Damage If the lid is continually banged shut it may damage the illumination tubes posioned inside the lid.	As above	Lid is solid and robust	2	3	Medium/ low	As above Equipment must be regularly checked and maintained. A log book should be kept to record maintenance carried out Equipment must be electrically tested at least every 3 years.

HEALTH & SAFETY ASSESSMENT

HAZARDS IDENTIFIED	PERSONS AFFECTED	EXISTING CONTROL MEASURES	LIKELIHOOD (1-5)	SEVERITY (1-5)	RISK RATING	ADDITIONAL CONTROL MEASURES
Hazardous Substances Methylene Blue and Plasma solution Leakage or failure of the bag system Methylene Blue may irritate eyes if splashed directly May be harmful if ingested in quantity	As Above	Dry MB pill integrated in the bag system which dissolves within the bag system Bag system is not put under pressure while MB is in solution	3	2	medium	Standard Lab PPE to be worn

NAME OF ASSESSOR: Sarah Smith
Senior Health and safety Adviser

DATE OF ASSESSMENT: 16/08/00

7. Results of Hospital Survey

Although methylene blue treated fresh frozen plasma has been used widely in some countries in Europe for several years, the use of virally inactivated plasma in hospitals supplied by the NBS has been limited to use of commercially available solvent detergent plasma (the uptake of which by UK hospitals has been patchy and small) and treatment of a few named patients using methylene blue plasma produced by the Scottish Blood Transfusion Service (which does not incorporate MB removal). The requirement for future use of NBS produced methylene blue plasma in UK hospitals was therefore unclear.

A survey was undertaken by means of a questionnaire sent to the top 44 FFP users supplied by the NBS. Between them these hospitals account for 50% of NBS FFP usage. Twenty-six responses were received. The results are summarised below.

1. What % of adult FFP would you replace by MB FFP

- 10 hospitals want none whether or not MB removed
- 13 hospitals would replace a proportion ----- <5 % - 6 hospitals
  - 5-10% - 3 hospitals
  - 10-30% - 4 hospitals
- 1 hospital would replace 100%
- 1 hospital sent no figures and asked for central guidance

Only two hospitals felt that price would affect usage - demand would be lower in these hospitals if price band were higher. Some mentioned a possible role of NICE in the decision-making with regard to FFP. MB removal made little difference to demand for adult FFP.

2. What % of <u>neonatal</u> FFP would you replace by MB FFP ?

- 16 hospitals would replace standard FFP only if MB removed (presumably for all neonates)
- 1 would replace standard FFP whether or not MB removed
- 6 would continue to use standard FFP
- 1 does not treat neonates

3. What % cryoprecipitate/cryosupernatant would you replace if MB treated?

- 13 hospitals would replace none
- 7 would replace 5-10%
- 3 would replace 30-50%
- 1 would replace 100%
- 1 would replace all cryosupernatant
- 1 was not sure

4. If a fibrinogen concentrate became available, what % of cryoprecipitate would you replace?

- 3 would replace none
- 14 expressed interest, but 3 of those were concerned about cost
- other replies unclear or probably negative.

In summary, therefore, this small sample suggests that approximately 50% of hospitals may consider using MB FFP for a small proportion of their adult patients, and a larger number (approximately 60% of responses) would like to use it in all neonates. It is estimated that this could be equivalent to approx. 5 - 10% of total adult FFP and 50 -100% neonatal requirements nationally. Half would replace some or all cryoprecipitate with MB treated cryoprecipitate. MB removal was thought to be important for neonates but less so for adult treatment.

A further survey of 5 children's hospitals is ongoing.

8. Cost Analysis

The model assumes annual production of FFP at 350,000 units.

Level of Activity	10%	30%	50%	100%
Additional cost per unit of FFP	£46	£47	£48	£47

Modelling Assumptions

All of the figures have been based on an assumed production of 350,000 units of FFP per year. The costing of this option includes areas of operation that are new to the NBS. The figures included for these options are best estimates from the limited information available and from experience gained during the small scale trials at Leeds and Birmingham.

i) At 10% activity will be undertaken in 3 centres. Each of these centres will need 2 WTE additional members of staff.

ii) At 30% activity, 50% of the FFP producing centres would need building works circa £350,000 There would be a requirement for 1 additional Sterile Connecting Device machine per producing centre. There would be 2 additional members of staff.

iii) At 50% activity, 75% of the FFP producing centres would need building works circa £350,000 and each producing centre would need 2 WTE additional members of staff. There would be a requirement for 1 additional Sterile Connecting Device machine per producing centre.

iv) At 100% activity all of the FFP producing centres would need building works circa £350,000 and each producing centre would need 4 WTE additional members of staff. There would be a requirement for 2 additional Sterile Connecting Device machines per producing centre.
At 10% activity will be undertaken in 3 centres. Each of these centres will need 2 WTE additional members of staff.

9. Options Assessment

Centre Capability

Current centre FFP processing targets are given below.

Annual FFP Production

Leeds	23,000
West of Pennines	43,000
Sheffield	17,000
Newcastle	20,000
	103,000
Birmingham	33,000
Bristol/Plymouth/Oxford	39,000
Southampton	16,000
	88,000
South Thames	47,000
Brentwood	37,000
Colindale	39,000
	123.000
Total	314,000

A simple analysis of centre methylene blue capacity has been performed to estimate what resources each processing centre would require in order to manufacture :

a) up to 10% MB treated plasma.
b) up to 30% MB treated plasma.
c) 100% MB treated plasma.

The questions asked were :

- Assuming zonal alignments are still in place - at the stated percentage would you wish to produce MB FFP at this site?
- Will you require increased space for this level of production?
- Will you required additional staff at this level of production?
- Will you require additional sterile connection devices (or other equipment)?
- Will you need to alter processing shifts to deal with this level of production?

These estimates have been based on a written description of the process since the evaluations have only recently been completed. The results of the survey are shown in the table at the end of this section.

100%

At 100% methylene blue treatment most centres will require considerable capital investment to provide sufficient space to house and provide an appropriate environment for the Macotronics and the additional peripherals such as sterile connecting devices, filtration racks and freezers. In some centres, notably Bristol and Sheffield (and possibly others yet to be identified) this will mean additional building works external to the footprint of the processing laboratory and almost certainly external to the existing footprint of the centre. The timescales for this to occur are considerable and estimated to be 15 - 18 months.

The process when worked under the current time constraints for freezing will require an extension to the working day in most centres and also contribute to the space requirements for processing since the relatively short time available for processing a large quantity of product will require extra equipment (and therefore space) to ensure that time constraints can be complied with. The equipment requirement is considerably more than would be required if the NBS had the luxury of overnight hold of product prior to freezing or the ability to use the freeze-thaw method employed by Grifols since this would allow the processing departments to spread the work over a greater time period.

10%

Most centres believe they can manage production of up to 10% methylene blue treated plasma with minimal impact. It should be noted however that because of the physical size of the Macotronic illumination machines even where additional space is not required, some element of refurbishment will be required to enable the equipment to be sited within existing processing areas. An assessment will also be required of the capability of the air conditioning units within the proposed areas since the Macotronics require a cooled environment for optimum operation even though they are provided with internal cooling mechanisms. There will be minimal impact on staffing, (refer to attached chart) and shifts at this level of activity which will obviously speed up implementation if the NBS decides this level of activity is an appropriate level. It is likely that as some machines ar already in situ this could be achieved within 3 - 6 months.

In all centres additional freezer storage is likely to be required even at this low proportion to enable segregation of the MB-treated FFP from standard FFP.

30%

At 30% the changes are obviously somewhere between the extremes quoted above. It should be noted however that the 30% level (more likely somewhere between 20 - 30%) is the breakpoint between what can be done with minimal impact and the level of activity needs a 'step-change' increase in resources, particularly with regard to premises. From the user survey carried out however it is unlikely that our present production

requirements will be at this level and this is discussed briefly in a previous section (7).

Effect of user requirements

From the results of the hospital survey it is apparent that there is no consensus on what our users require with regard to this product and from the figures quoted it would seem that an average figure of 5% (+ neonatal FFP) would be an appropriate starting level of activity. At this level it becomes a realistic option to centralise all production of MB-treated FFP on a few sites possibly based around the former zonal groupings and particularly on the sites currently having experience of this procedure (Birmingham and Leeds) plus a centre in the L&SE zone.

The table below gives worked examples for each zone :

Northern Zone total adult FFP = 103,000
5% of the NZ total = 5,150

This represents 22% of Leeds total adult FFP production

Midlands and South West total adult FFP = 88,000
5% of the M&SW total = 4,400

This represents 13% of the Birmingham total adult FFP

London and South East total FFP =123,000
5% of the L&SE total = 6,150

This represents 13% of the South Thames total adult FFP

To these figures must be added the NBS requirements for neonatal FFP which is approx. 15,000 per annum. There would be additional work in terms of testing at each centralised site to ensure there were adequate levels of plasma suitable for neonatal use. Consideration should be given to the use of apheresis to meet the requirement for neonatal plasma, particularly group AB although this would require some major re-distribution of apheresis platelet capacity between centres.

To provide this level of production on a centralised basis, with the current process constraints for plasma, and the experienced throughput of the illumination device, it is estimated that there would be a requirement for 2 maco-tronic machines and two additional members of staff dedicated to this process at each site (based on centre questionnaire).

If additional evaluation work removed the time constraints it would be feasible to manage the process with a single machine per site but the staffing requirements would remain the same.

Whilst the user requirements remain so low , consideration should be given to consolidation of MB processing on fewer sites to minimise general disruption at all blood centres and to allow resources to be used more effectively.

In the event that such an option was chosen it must be remembered that the MB processing sites would potentially need to be resourced with standard FFP to compensate for their additional MB treated FFP production. Likewise the NBS would need to consider the requirement for couriers or NBS transport for transferring MB-treated FFP to other sites on a regular basis.

This would have a significant impact on Issue departments. This option would require fairly large scale transfer of frozen components between blood centres, impacting on the staff of the exporting site as the logging out and packaging of FFP is quite a lengthy process and some consideration should be made for additional resource to support this activity (e.g. 1 wte). In addition, it should be noted that the frozen plasma packs are extremely fragile, current rate of breakage are approx. 5%, with some centre to centre variation. This could be expected to increase due to the additional handling of the components. Some additional time would be required during any implementation period to evaluate packaging and transport processes.

From this work it must be emphasised that in setting up the MB process to meet expected hospital demand, only very small increases in that demand can be met without significant additional resource, staff, equipment and buildings, and there would be inevitably a prolonged lag phase in the ability of the NBS to supply.

Centre resource summary

			Production at this site?	Space required?	Staff wte required	SCD's required ?	Shifts need to be changed ?
	South Thames	10%	Y	N	1	1	N
		30%	Y	N	2	2	Y
		100%	Y	Y	4	4	Y
	Brentwood	10%	Y	N	1	1	N
		30%	Y	N	2	1	Y
		100%	N	Y	4	3	Y
	N. London	10%	Y	N	1	1	N
		30%	Y	N	2	1	Y
		100%	Y	N	4	3	Y
	Birmingham	10%	Y	N	1	1	N
		30%	Y	N	4	2	Y
		100%	Y	Y	7	4	Y
	Bristol	10%	Y	Y	1	1	N
		30%	Y	Y	2	3	Y
		100%	Y	Y	10	5	Y
	Southampton	10%	N	-	-	-	-
		30%	N	-	-	-	-
		100%	Y	Y	4	2	Y
	Leeds	10%	Y	N	1	1	N
		30%	Y	N	2	1	N
		100%	Y	N	4	2	Y
	Sheffield	10%	Y	Y	1	1	N
		30%	Y	Y	2	1	N
		100%	N	-	-	-	-
	Newcastle	10%	Y	N	2	1	N
		30%	Y	Y	3	2	N
		100%	Y	Y	4	3	Y
	Manchester	10%	y	y	2	1	N
		30%	y	y	4	1	N
		100%	y	y	7	2	N

10. Summary

The scientific and operational evaluations of the Macopharma MB system coupled with MB removal using the Pall filtration system have shown that components can be produced under routine operating conditions which meet the current specification for Methylene Blue plasma as required by the UKBTS Guidelines (4th edition). The guidelines do not provide a specification for MB removal and to date it has not been possible to find a simple assay to monitor this process in routine practice.

The process has been shown to be time-consuming, and at all but very limited production levels has a significant impact on blood centres in terms of staff, equipment and buildings. The evaluations have raised a number of issues with the MB system, primarily around plasma volume, loss of coagulation activity related to initial pack types, assurance of the actual inactivation procedure, solubility of the MB pellet and time constraints on the actual process.

On the question of volume, it would be necessary to standardise, as far as is practicable, on plasma volume in order to ensure compliance with the range recommended for the procedure. This would require an evaluation and modification of existing procedures used at blood centre and some control built in to the MB procedure to facilitate selection of appropriate components for treatment.

The phase 0 evaluations (and subsequent routine trials) have indicated that there is a considerable loss of coagulation activity due to MB treatment and this makes the choice of starting plasma important so as not to compound these losses further. Filters used to leucodeplete are known to have differential effects on coagulation factor removal, and therefore it would be preferential to use only non-leucodepleted plasma as a start product. If this is not possible, then plasma should be obtained after filtration with a filter which has been demonstrated to have minimal effect on plasma quality. The system recommended in this case is the Baxter whole blood filtration system. If pre-leucodepleted plasma has to be utilised it is essential, therefore, that the appropriate mix of collection systems are used at the sites used for the MB treatment process.

There is some limited data (one blood centre, Barcelona) to show that there may be a subsequent rise in the use of plasma (and potentially cryoprecipitate) following the implementation of MB treatment. Although, this is not proven it should be given some consideration when determining the volume of MB plasma to be produced.

During the phase 1 and 2 evaluations concern was raised concerning assurance that the plasma had received the correct exposure, in fact, there is no positive check that the plasma has actually been placed in the illumination device. The pack donation numbers are entered into the controlling PC and a printout is produced at the end of the cycle linking the

unit to an assessment of exposure. Although, a positive indicator, for example an indicator label, or in fact a direct output to Pulse, would be a useful addition, the process can be controlled through appropriate procedural safeguards, ensuring dedicated, trained staff are available to operate and monitor the system at all times.

This same degree of procedural control is essential to monitor the MB addition phase, to ensure that the pellet dissolves completely prior to the illumination phase, and that any failures are identified and discarded using the appropriate procedures.

Current time constraints on the processing of plasma and subsequent MB treatment pose a significant obstacle to increasing MB plasma production above minimal levels. If there is to be any move to the implementation of this process it is recommended that further work is undertaken to evaluate the Macopharma MB process using plasma which has been frozen and thawed, and/or plasma which has been separated from whole blood after an extended hold period, for example, overnight at 4°C. If successful, this would extend the processing window for this product.

It should be noted that a limited amount of work has been carried out by both the NBS and SNBTS which has indicated that Cryoprecipitate can be successfully prepared using methylene blue treated plasma. This was carried out using the Baxter Pathinact system for MB treatment which is essentially the same as the Macopharma system, both using methodology developed by Springe. A larger scale evaluation involving routine production would be advisable if the MB process is to be considered.

To summarise, the Macopharma MB system with additional removal is considered suitable for the routine, in house, production of Methylene Blue viral inactivated plasma, providing appropriate procedural control is built in to the process and dedicated, well trained staff are provided to operate and monitor the system. It is possible to implement on a small scale to meet the expected demand from user hospitals (based on the User survey), of approx. 5% adult dose and 100% neonatal. This could best be achieved by centralising production on three main centres with minimal outlay in terms of building works and a small number of additional staff, both for processing and to support the issue and packaging for transport to other centres. Additional transport systems would have to be implemented to complement the centralised production.

It is possible that increases in user demand up to 20% (including Neonatal) could be accommodated with minimal impact, some additional staff and equipment. Above this level of activity there is a major step-change which would require implementation of the system on more sites, with consequent considerable capital investment required to provide sufficient space to house and provide an appropriate environment for the Maco-tronics and MB procedures.