



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Consultation procedure Public Assessment Report (CPAR)

Consultation on an ancillary medicinal substance incorporated in a medical device

Medical device: Irvine Scientific

Ancillary medicinal substance: Reproductive Media Products containing Human Tissues/Plasma

EMA/H/D/866

Applicant: NSAI (National Standards Authority of Ireland)

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted



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Administrative information

Invented name of medical device:	Reproductive Media Products containing Human Tissues/Plasma
INN (or common name) of the ancillary medicinal substance:	Human Albumin Solution
Applicant for medical device CE certification:	Irvine Scientific
Notified body:	NSAI (National Standards Authority of Ireland)
Applied intended purpose of the device:	The Reproductive media are intended for use in the washing of human sperm, culturing and cryopreservation of specimens for use in assisted reproductive technology procedures.
Intended purpose of the ancillary medicinal substance in the device:	<ul style="list-style-type: none"> a) To prevent the gametes and embryos becoming sticky, b) To facilitate manipulation of the gametes and embryos, c) To negate the effects of toxins, d) To include fatty acids and citrate in the media which have both been shown to be embryonic factors which stimulate cleavage and growth in rabbit morulae and blasts.
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	5-50 mg/ml

1. Background information on the procedure

1.1. Submission of the dossier

The Notified Body NSAI (National Standards Authority of Ireland) submitted to the European Medicines Agency (EMA) on 02.05.2007 an application for Consultation on Human Albumin Solution as ancillary medicinal substance(s) used in a medical device Reproductive Media Products containing Human tissues/Plasma, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. Ian Hudson Co-Rapporteur: Dr. Christian Schneider

1.2. Steps taken for the assessment of the product

- The application was received by the EMA on 02.05.2007.
- Additional information was submitted on 09.07.2007
- The procedure started on 19.07.2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8.10.2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11.10.2007.
- During the meeting on 12-15.11.2007, the CHMP agreed on the consolidated List of Questions to be sent to the Notified Body. The final consolidated List of Questions was sent to the Notified Body on 16.11.2007.
- The Notified Body submitted the responses to the CHMP consolidated List of Questions on 20.12.2007.
- The Rapporteurs circulated the Joint Assessment Report on the Notified Body's responses to the List of Questions to all CHMP members on 06.02.2008.
- During the meeting on 18-21.02.2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the quality, safety and usefulness of Albumin Human Solution as ancillary medicinal substance(s) used in the Reproductive Media Products containing Human tissues/Plasma manufactured by Irvine Scientific.

2. General conditions for the use of ancillary medicinal substances in medical devices

2.1. Manufacturers

Manufacturer of the active substance used as ancillary medicinal substance

Talecris Biotherapeutics, Inc
86368 US 70 West Clayton, North Carolina 27520, USA

Manufacturer responsible for import and batch release in the European Economic Area

Talecris Biotherapeutics (former Bayer Biologicals S.r.l)
Bellaria 35 I-53010, Torri-Sovicille (SI), Italy

Manufacturer(s) of the device(s)

Irvine Scientific
2511 Daimler Street, Santa Ana, CA 92705-5588, USA

In accordance with Council Directive 93/42/EEC, as amended, a sample from each batch of bulk and/or finished product of the human blood derivative shall be tested by a State laboratory or a laboratory designated for that purpose by a Member State.

2.2. Recommended measures to the Notified Body

None

3. Scientific discussion

3.1. Introduction

The Reproductive Media Products containing Human Albumin manufactured by Irvine Scientific are classified as a medical device according to the relevant Commission Directive 93/42/EEC. The Irvine solutions incorporate human albumin solution as a medicinal substance with ancillary action. The Notified Body National Standards Authority of Ireland (NSAI) is consulting the CHMP regarding the quality, safety and usefulness of the albumin component in the Reproductive Media Products containing Human tissues/Plasma from Irvine Scientific according to Directive 2000/70/EC.

Irvine Scientific provides a complete range of media products intended for use in assisted reproductive procedures. Irvine Scientific media include 19-different albumin containing solutions designed for use in the following procedures: washing of human sperm, culturing, manipulation and cryopreservations of specimens for use in assist reproductive technology procedures.

The intended purpose of the range of reproductive media containing human albumin of Irvine Scientific is the 'in vitro' maturation, culture and cryopreservation of human gametes and embryos.

The albumin human solution used for this purpose is Human Albumin 25% L/A (low aluminium) from Talecris. The albumin is licensed in Germany and Greece under the names of Plasbumin and Human Albumin Bayer respectively. Human albumin is used as a supplement in the media solutions for a number of reasons: to prevent gametes and embryos from becoming sticky, to counteract the effects of toxins and also it binds fatty acids and stabilizes other growth-promoting substances. Human albumin is used in cryopreservation as an osmolyte in media to minimise osmotic shock and solute effects when manipulating the embryo in vitro. It also coats the surfaces of laboratory equipment such as culture dishes and pipettes which are used in ART and prevents attachment of sperm, oocytes and embryos.

Human Albumin L/A 25% is manufactured according to Cohn-Oncley fractionation and in compliance with the Ph. Eur. monograph "Human Albumin Solution". The plasma used for the production of Human Albumin L/A 25% is covered by Talecris's Plasma Master File (PMF), which is assessed in the centralised PMF certification process. The initial PMF certificate was issued in February 2005 and last updated in November 2007.

Composition and intended use of the albumin containing solutions of the medical device

Product Name	Catalogue Number	Intended Purpose	Principle mechanism of action
Dextran Serum Supplement (DSS)	9301	Supplements culture media for ART procedures which include gamete and embryo manipulation.	Prevents gametes and embryos from becoming sticky which facilitates manipulation. Provides embryotrophic factors. Binds lipids. Binds and stabilises growth factors.
Complete Human Tubal Fluid (HTF) Medium with Dextran Serum Supplement (DSS)	9900	A culture medium for fertilisation and culture of human embryos through day 3 of development.	Provides a physiological environment for growth of human embryos
Complete P-1 Medium with Dextran Serum Supplement	9910	A culture medium for fertilisation and culture of human embryos through day 3 of development.	Provides a physiological environment for growth of human embryos.
Complete Blastocyst Medium with Dextran Serum Supplement	9915	A culture medium for human embryos from day 3 to the blastocyst stage of development.	Provides a physiological environment for growth of human blastocysts.
Product Name	Catalogue Number	Intended Purpose	Principle mechanism of action
Sperm Washing Medium	9983	A medium used for sperm washing procedures.	Provides a physiological environment for washing of human sperm.
Hyaluronidase Solution	90101	A solution used for removing cumulus cells surrounding oocytes in preparation for Intra-Cytoplasmic Sperm Injection (ICSI) or other ART procedures.	Enzymatic digestion of hyaluronic acid which keeps the cumulus cells aggregated around the oocyte.
Embryo Biopsy Medium	90103	Culture medium used when performing embryo biopsies on cleavage stage (4-10 cell) human embryos to remove blastomeres for Pre-Implantation	Provides a physiological environment for the growth of human embryos following the removal of cells

		Genetic Diagnosis (PGD)	during PGD.
Blastocyst Freeze Kit – contains 2 media: Blastocyst Freeze – F1 Blastocyst Freeze – F2	90108 90100 90102	Kit is composed of 2 media, F1 and F2 which are to be used sequentially in the cryopreservation of blastocysts.	Dehydration of the blastocysts to remove water from the cells and replace it with the cryoprotectants.
Blastocyst Thaw Kit – contains 2 media: Blastocyst Thaw – T1 Blastocyst Thaw – T2	90110 90104 90106	Kit is composed of 2 media, T1 and T2 which are to be used sequentially in the thawing of cryopreserved blastocysts.	Removal of the cryoprotectants and rehydration of the blastocysts.
Embryo Freeze Media contains 2 media: Embryo Freeze – F1 Embryo Freeze – F2	90116 90112 90114	The kit is composed of two media that are to be used sequentially in the cryopreservation of embryos. The media in the kit contains propanediol that are supplemented with human serum albumin.	Dehydration of the embryos to remove water from the cells and replace it with the cryoprotectants.
Embryo Thaw Kit – contains 3 media: Embryo Thaw – T1 Embryo Thaw – T2 Embryo Thaw – T3	90124 90118 90120 90122	Kit is composed of 2 media, F1 and F2 which are to be used sequentially in the thawing of embryos.	Removal of the cryoprotectants and rehydration of the embryos.
Vitrification Freeze Kit – contains 2 media: Equilibration Solution (ES) Vitrification Solution (VS)	90133 90131 90132	Kit is composed of 2 media, F1 and F2 which are to be used sequentially in the vitrification of oocytes and blastocysts.	Dehydration of the oocytes and blastocysts to remove water from the cells and replace it with the cryoprotectants.
Vitrification Thaw Kit – contains 3 media: Thawing Solution (TS) Dilution Solution (DS) Washing Solution (WS)	90137 90134 90135 90136	Kit is composed of 2 media, F1 and F2 which are to be used sequentially in the thawing of vitrified oocytes and blastocysts.	Removal of the cryoprotectants and rehydration of the embryos and blastocysts.
Product Name	Catalogue Number	Intended Purpose	Principle mechanism of action
Complete Early Cleavage Medium with Dextran Serum Supplement (DSS)	90142	A culture medium for human embryos through day 3 of development.	Provides a physiological environment for the growth of human blastocysts.
Complete MultiBlast Medium with Dextran Serum	90143	Complete medium for human embryos from day 3 to the blastocyst	Provides a physiological environment for

Supplement (DSS)		stage of development.	the growth of human blastocysts.
Modified Ham's F-10	99109	Used for sperm washing procedures.	Provides a physiological environment for sperm during washing.
Sperm Maintenance Medium	99176	Used for cryopreservation and storage of human sperm.	Dehydration of sperm to remove the water from them and replace it with the cryoprotectants.
7% Polyvinylpyrrolidone	90121	Used for immobilising sperm for ICSI procedures.	Viscous solution to immobilise sperm
10% Polyvinylpyrrolidone	90123	Used for immobilising sperm for ICSI procedures.	Viscous solution to immobilise sperm

3.2. Medicinal product before incorporation in the medical device

Quality Aspects

Introduction

Albumin 25% L/A is a clear, slightly viscous pale yellow to amber coloured liquid. The active substance is human albumin. The albumin content in the product is not less than 96%. The composition is formulated to comply with the Ph.Eur. monograph 'Human Albumin Solution'.

Excipients

Sodium caprylate and N-acetyl-DL-tryptophan are used as excipients to stabilise the albumin and to reduce the formation of aggregates.

Specifications for N-acetyl-DL-tryptophan and sodium caprylate were provided and comply with Ph. Eur.

Container Closure System

The container consists of glass vials. The stoppers are made of a halo butyl isoprene-blend elastomer.

Drug Substance

For the purpose of this report, the drug substance is defined as the sterile albumin bulk material prior to sterile filling.

Manufacture Nomenclature

The Ph. Eur. name of the active ingredient is Human Albumin Solution (Albumini Humani Solutio).

Structural Formula

A short description of the albumin molecule has been provided. Albumin consists of one single polypeptide chain of 585 amino acids cross linked by 17 disulfide bridges. The protein has a high degree of alpha helical structures and is folded into three domains. Each cylinder like domain has a

hydrophobic inner space where hydrophobic substances such as fatty acids can bind. The outer surface of the molecule is mainly polar.

General Properties

The active substance human albumin is derived from human plasma.

Definition of a batch

A fractionation batch is defined as the final Fraction V paste which is derived from Cohn fractionation of an amount of starting plasma.

A purification batch is defined as the final albumin bulk derived from the purification of an amount of Fraction V paste. The final bulk is sterile and contains stabilisers and electrolytes. A typical batch size is approximately 800 kg.

Description of Manufacturing Process and Process Controls

The manufacture of the sterile bulk is basically performed in two separate sequential processes: Cohn-Oncley fractionation followed by further purification steps.

The fractionation is a well-established method and consists of steps from plasma pooling to final Fraction V step. A series of cold alcohol precipitation steps, in which differences in pH, temperature and alcohol concentration are used, to separate the different protein fractions in plasma to obtain fraction V paste.

The purification consists of steps from suspension of fraction V paste to the sterile bulk and follows a series of standard pharmaceutical industry unit processes which include low temperature, pH control, filtration, centrifugation and acetone suspension.

There is no reprocessing of any of the fractionation steps. According to the manufacturer, in some cases, there is an option for reprocessing/reworking of the final bulk solution in case a compromise in bulk sterility occurs.

Control of materials

The Plasma Master File (PMF) covering the human plasma for fractionation used as starting material has already been approved in the centralised PMF certification procedure. Talecris PMF (formerly Bayer PMF) first certificate was granted for the PMF in February 2005 (EMA/H/PMF/000004/04) and was re-certified in November 2007 (EMA/H/PMF/000004/04/AU/006). Only plasma certified by the centrally approved PMF is used for the production of human albumin incorporated in the in vitro fertilisation media.

The safety of the albumin with regard to potential Parvovirus B19 transmission requires special consideration. The applicant proposed a limit for parvovirus B19 for the production plasma pool. The limit is considered acceptable to guarantee the safety of the albumin taking into account the parvovirus clearance of the manufacturing process of the albumin as discussed in the Adventitious Agent Safety Evaluation section of this report.

All raw materials used in the fractionation and purification steps of the manufacturing process meet the requirements of the European Pharmacopoeia (Ph. Eur.) and/or the United States Pharmacopoeia (USP). The specifications established by Talecris Biotherapeutics (formerly Bayer) have been provided. No animal derived materials are used in the manufacture of human albumin.

Control of Critical Steps and Intermediates

The control of the manufacturing process is deemed acceptable and relevant in-process controls are in place.

Microbiological quality is monitored throughout processes to ensure the necessary controls are in place to minimize potential product contamination. Information on all processing steps/conditions, the specification limits, reaction times, viral removal capacity and options for process-interruptions or storage time of intermediates are sufficiently provided.

Process Validation

The manufacturing process beginning with the plasma pool through to the sterile filtered bulk has been sufficiently validated and consistency of the production process has been adequately demonstrated. At least three consecutive qualification runs were performed for each system of the albumin product stream. Performance qualification of the process was carried out using approved batch production records.

Critical process steps, operating parameters and intermediate test data were evaluated to determine that each process step was consistent and that the final output of each process system met a set of pre-established acceptance criteria. All acceptance criteria were met and the performance qualification demonstrated that the manufacturing process produces intermediates and final product that meet the pre-determined specifications and quality attributes.

Manufacturing Process Development

The method developed by Cohn for the cold ethanol fractionation of plasma to albumin was first published in 1946. Since that time a number of modifications have been introduced. These include changing the ethanol concentration to increase efficiency of the process, acetone drying of the albumin powder to reduce drying time and remove unwanted lipids, incorporation of a pasteurisation step and the inclusion of caprylate as a stabiliser.

Impurities

More than 30 lots from each tested intermediate were analysed for the fractionation and purification steps of the process and the results verified consistency and reproducibility of the production process. The applicant has demonstrated the removal of expected impurities in the starting material as well as process related impurities.

Specification

The sterile bulk before filling specification has been set at not less than 96% albumin. Protein composition of the drug substance is determined. The method has been validated and full details have been provided.

Data from three batches were provided and all results complied with the set specification.

Container closure system

Sterile bulk solution before filling is stored in sterile stainless steel tanks in Class C conditions under positive air pressure and vented through a filter.

Stability

The stability studies of the finished product support the current shelf life of the active substance and the intermediates.

A protocol has been submitted for a proposed stability study designed to monitor the intermediates and the active substance.,

The integrity of the storage system has been verified .

Drug Product

Pharmaceutical Development

The Cohn fractionation of human plasma to albumin was first described in 1946. Modifications have since been introduced including the use of pasteurisation and the inclusion of caprylate as a stabiliser of the albumin protein.

Most of the description of pharmaceutical development is based on literature data since the Cohn-Oncley process is a well-established process. The excipients used are also well known and it is therefore acceptable that the applicant refers to the literature.

Albumin 25% L/A is supplied in glass vials together with stoppers which are made from a halobutyl isoprene-blend elastomer formulation. Safety of the closure system has been demonstrated by data on the stopper composition and data on aqueous extraction and toxicological studies.

The integrity of the closure system has been demonstrated by a leakage test and stability studies.

Batch formula

A batch is defined as the final uniform albumin bulk derived from the purification of an amount of fraction V paste.

Description of the manufacturing process and in-process controls

Production of the drug product from sterile albumin bulk consists of aseptic filling into final container, pasteurisation, incubation of final container after which the vials are stored. A flow chart of the process has been provided.

Reprocessing of the bulk is allowed when a compromise in bulk sterility is suspected caused by operator or equipment error.

The product is packaged for export and a description of the packaging procedure has been provided. All final container units are 100% visually inspected against a light and dark background for bottle integrity and defects in product content. Final labelling is carried out in Italy.

Process validation

Full descriptions of the validation of procedures and equipment have been provided. The clean rooms are GMP certified.

Control of excipients

Specifications for N-acetyl-DL-tryptophan and sodium caprylate used as stabilisers in the finished product were provided. Both specifications comply with Ph. Eur.

Product Specification

Methods used for the release of the drug product are either Ph. Eur. methods or equivalent to Ph. Eur. methods. Validation reports were provided for test methods which are not performed according to the Ph. Eur. methods.

Container Closure System

The container consists of bottles of glass and isoprene rubber blend stoppers are used as closure. Both bottles and stoppers meet the requirements of the Ph. Eur. An crimp cap is also used to seal the stoppers.

Stability of the Product

Results from four manufacturing batches support the assigned shelf life of 36 months under storage at a temperature not exceeding 30°C. The end of shelf life acceptance criteria ensure continued

compliance with the Human Albumin Solution monograph of the European Pharmacopoeia, and are **generally the same as the release criteria.**

Facilities and Equipment

A detailed description of the production facilities has been provided. The facility has undergone complete validation and is operated in accordance with current GMP. The buildings and equipment used to produce the product are dedicated to plasma product production.

Adventitious Agents Safety Evaluation

Adventitious Agents

No materials of bovine or other TSE-susceptible animal species are used in production.

The Albumin 25% is produced from human plasma. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. The exclusion criteria have been described in the Plasma Master File (PMF) and were considered adequate and in line with Position Statement CPMP/BWP/2879/02. Intermediates of other suppliers are not used for production of the drug product.

The manufacturing process was investigated on its capacity to remove TSE agents. These investigational studies provide evidence that significant removal of prions can be expected from the manufacturing process.

Adventitious Viruses

Four steps of the production process were extensively validated for their virus inactivation/removing capacity.

A report has been provided which details the viral safety measures incorporated into the albumin process. These include donor screening, testing of plasma donors and plasma manufacturing pools, a 60 day hold for donations and the virus clearance validation studies carried out on the albumin manufacturing process. These validation studies include an evaluation of the clearance of the model virus Porcine Parvovirus which is highly resistant to physico-chemical treatments, in contrast to the human parvovirus B19 which literature references suggest is rapidly inactivated by the standard albumin pasteurisation process. The results of the virus validation studies showed a 6.8 log reduction of PPV.

The plasma pools used for manufacture are also tested for B19. Using this information and the reduction factor obtained from the validation studies, Talecris has estimated the potential number of virus particles in a final container of 25% albumin to be 4.4×10^{-1} particles per ml.

In the risk assessment the applicant states that a conservative approach has been taken in using viral genomes as an indicator of potentially infectious viral particles since the virus titres determined by NAT do not differentiate between infectious and non-infectious particles. Literature references have been provided and indicate that $\square 10^4$ genome equivalents of B19 DNA were required to produce seroconversion of individuals receiving parentally-administered plasma-derived medicinal products.

According to this data, the limit set for the plasma pools is considered acceptable to guarantee the safety of the albumin and the virus safety of albumin 25% has been adequately demonstrated.

Talecris has confirmed that each batch of final product can be traced back to the individual donations used for its manufacture and viceversa. There is a link through the manufacturer of the human albumin to post collection information on the donors and to post marketing data on the albumin and its starting plasma pool until the expiry date of the medical device containing albumin.

Discussion on chemical, pharmaceutical and biological aspects

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines and Ph. Eur. monograph for human albumin. The information provided in the application showed a consistent batch-to-batch production of Human Albumin L/A 25% achieving an adequate quality for the drug substance and the drug product. The manufacturing process of the drug substance and drug product were described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications.

The capacity and robustness of the manufacturing process to inactivate and remove viruses has sufficiently been investigated and, in summary, the virus safety of Human Albumin L/A 25% has adequately been demonstrated. No materials of bovine or other TSE-susceptible animal species are used in production. The Human Albumin L/A 25% is produced from human plasma. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. In addition, investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process.

3.3. Medicinal product in the context of its use in the medical device

Introduction

Irvine Scientific reproductive media are comprised of 19 different albumin-containing media used for handling gametes and embryos during In Vitro Fertilisation (IVF) and contain a protein supplement for culture medium. This protein supplement is human albumin, which has an ancillary effect, with the purpose to assist the function of the medical device.

The quality, safety and usefulness of the albumin as component of the solution are evaluated in the following part of the CHMP assessment report.

Quality, Safety and Usefulness

- General Information

The reproductive media of Irvine Scientific consists of several solutions or kits of solutions intended for use during the different stages of assisted reproductive techniques (ART) such as gamete and embryo manipulation, culture and storage. The solutions are supplemented with Human Albumin at the production site. The concentration of Human Albumin in the various solutions varies from 5 mg/ml to 50 mg/ml. There is no manipulation of the Human Albumin before adding it to the medical device solution. The Human Albumin used as ancillary medical substance is Human Albumin L/A 25% from Talecris and is manufactured according to the Ph Eur monograph Human Albumin Solution.

The Irvine Scientific reproductive media containing human albumin are designed for use in the following ART procedures: washing of human sperm, culturing, manipulation and cryopreservations of specimens for use in assisted reproductive technology procedures.

The intended purpose of the range of reproductive media containing human albumin of Irvine Scientific is the 'in vitro' maturation, culture and cryopreservation of human gametes and embryos.

The role of the albumin in the media is extensive. Albumin is intended to prevent gametes and embryos from becoming sticky, it may counteract the effects of toxins and also it binds fatty acids and stabilises other growth-promoting substances. Human albumin is used in cryopreservation and as an osmolyte in media to minimise osmotic shock and solute effects when manipulating the embryo in vitro. It also coats the surfaces of laboratory equipment such as culture dishes and pipettes which are used in ART and prevents attachment of sperm, oocytes and embryos.

The function of albumin in all the reproductive media solutions is as an ancillary substance.

- Qualitative and quantitative particulars of the constituents

The concentration of human albumin in each media varies according to the intended use of the media.

- Description of method of manufacture

The production facility and its utilities have undergone complete validation and are operated in accordance with the ISO 13485, Quality Management Systems – Medical Devices – Systems Requirements for Regulatory Purposes and with the FDA’s Quality System Regulation, 21 CFR Part 820, Medical Devices; Current Good Manufacturing Processes.

The production of respective solutions is performed by adding different ingredients to water for injection, mixing, and filtration of the solutions. An overview of the manufacturing process was provided.

Formulation of the liquid media is carried out in an ISO Class 7 designated area using Water for Injection for each product formulation. The raw materials are specified on the manufacturing product formulation record by raw material part number, lot number, expiration date and location. The liquid media is subjected to in-process testing and test results must meet specifications before the filling process is initiated.

The liquid media is pumped into an ISO Class 6 clean room and into Class 100 laminar flow hoods where it is aseptically filled. Filter integrity testing is performed on each product filter when the filtration process has been completed.

Environmental monitoring is performed on each day of filling of product in the production clean room. Clean room monitoring includes air sampling for viable organisms, particle monitoring and surface sampling and is carried out in accordance with the relevant guidelines, including EN ISO 14644 -1 and EN ISO 14644-2 Clean rooms and Associated Controlled Environments Parts 1 and 2.

Filled containers leave the ISO Class 6 room and are labelled and packaged to be held in quarantine before final release. When final product testing has been completed for the product the batch history record is submitted to Quality Assurance for final product release and distribution.

- Controls of starting materials

The Human Albumin complies with the Ph. Eur. monograph on Human Albumin Solution, which specifies quality requirements for a product normally administered intravenously.

The albumin, as all raw materials is received, inspected and tested in accordance with the relevant raw material specifications. For human albumin, a Certificate of Analysis is required, confirming that the product is non-reactive at the donor level for HIV antibody, HCV and HBsAg. ‘In-house’ testing is also carried out on each lot of human albumin .

The Shelf Life specifications for Human Albumin 25% have been provided. The applicant confirmed that the expiry dates of albumin solutions are later than those of the media in which they are incorporated.

The applicant provided a flow chart describing the process of inclusion of EEA batch released human albumin in the medical device in the US.

The manufacturers of the Human Albumin solution and the medical device committed that only Official Control Authority Batch Release (OCABR) lots of Human Albumin L/A 25% solution will be used for manufacture of the device.

The several other media components are purchased from approved, qualified suppliers. They are stated to be of Ph.Eur. monograph quality where possible, or to satisfy in-house or supplier acceptance criteria. Raw materials are received, inspected and tested in accordance with the relevant raw material

specifications. The water used for cleaning and formulating meets Ph.Eur. and USP requirements for Water for Injection.

- Control tests carried out at intermediate stages of the manufacturing process of the medical device

Not applicable.

- Control tests on finished product

Additional analyses are conducted on media depending on their intended function.

A test for albumin concentration as part of release testing was developed . The method was validated and is considered to be acceptable for the measurement of albumin concentration.

- Stability

Real time and accelerated stability were carried out on all the albumin-containing media solutions. The products were tested according to release specifications and some products were tested against additional parameters. The stability parameters are identical with the corresponding finished product specification.

In addition an open container study was carried out.

The concentration of albumin was measured in samples of each media product after the expiration date of the product by the same dye binding assay used at batch release.

Stability testing has also been carried out on the incoming human albumin at 3 years 7 months and 5 years after the date of receipt. There were no significant changes in any of the parameters and the albumin met the raw material specifications for 6 years 2 months after manufacture.

- Toxicity

Human serum albumin is a well known substance which has been used for over 50 years. It has been used in IVF media for over 20 years and is not associated with embryo-foetal toxicity, oncogenicity or mutagenic potential. A review has been provided of the published safety and toxicity data for human albumin.

The EMEA Document CPMP/PhVWP/BPWG/2231/99 rev.2 "Core SPC for Human Albumin Solution" states that:

- 1- Human albumin is a normal constituent of human plasma and acts like physiological albumin
- 2- To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.
- 3- No signs of acute toxicity have been described in animal models.

- Reproductive function

No studies have been performed. However, human serum albumin is a well known substance which has been used for over 50 years and is not considered a reproductive toxicant.

- Embryo/foetal and perinatal toxicity

A review has been provided of the literature describing the use of human albumin in the development of media for the culture of human embryos. Human Albumin is considered to be a necessary component for this practice. Moreover, the Core SPC for Human Albumin (CPMP/PhVWP/BPWG/2231/99 rev.2 states that: 'To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential'

- Mutagenic potential

No studies have been performed. Anyway, the Core SPC for Human Albumin (CPMP/PhVWP/BPWG/223/99 rev.2 states that: 'To date, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential'

- Carcinogenic potential

No studies have been performed.

Carcinogenicity is not considered a relevant test in the ISO 10993-1: 2003 Standard for devices with limited exposure to the patient.

Furthermore, the EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 "Core SPC for Human Albumin Solution" specifically states that "to date, human albumin has not been reported to be associated with oncogenic potential".

- Pharmacodynamics

Human albumin accounts qualitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity in the liver. The most important physiological functions of human albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilizes circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins. The role of protein in embryo culture medium may not only be as nitrogen source, but also as chelator to toxic metal ions. Human albumin binds other components and presents them to the embryo (transport protein), a source of amino acids, small ionic molecules and lipids, binds toxic species and sustains embryo growth.

- Pharmacokinetics

Not applicable.

- Local tolerance

The EMEA Guideline CPMP/PhVWP/BPWG/2231/99 rev.2 states that "to date, human albumin has not been reported to be associated with embryo-foetal toxicity".

Moreover, a sensitization study was performed in mice using a Murine Local Lymph Node Assay, in accordance with ISO 10993 Biological Evaluation of Medical Devices Part 10. None of the samples tested were found sensitising to the mice.

In addition, reference has been made to the review provided of the published safety and toxicity data for human albumin.

- Clinical documentation

The Irvine Scientific Reproductive Media Products culture media have been designed for use in ART procedures to mimic the physiological conditions required for storage, manipulation and transfer of gametes, embryos or sperm. In these solutions human albumin, supplied by Talecris Biotherapeutics, functions as an ancillary substance.

The clinical evaluation report submitted by the applicants reviews the literature supporting the use of human albumin in IVF media solutions.

Three main studies cited in the review are summarised below.

Stassen et al. performed a comparison between human serum and Albuminar -20™, a human serum albumin product manufactured by Armour Pharmaceutical as a supplement for in-vitro fertilization. The fertilisation rates of oocytes and spermatozoa cultured in these two samples were similar. The embryos after further culture in Albuminar-20 had higher morphological quality cleaved embryos which correlated with a higher pregnancy rate.

Laverge et al. conducted a study comparing human serum albumin with foetal cord serum as a protein supplement in culture medium. A prospective randomized study was performed of patients undergoing IVF or intracytoplasmic sperm injection (ICSI) where embryos were cultured in Earle's balanced salt solution containing either 8% (v/v) foetal cord serum or 0.4% (w/v) human serum albumin as a protein source. Fertilization rates, morphological embryonic quality and pregnancy rates were compared. A total of 2189 oocytes from 210 cycles were cultured in medium supplemented with human serum albumin in patient group 1 and 2109 oocytes from 203 cycle in medium supplemented in foetal cord serum in patient group 2. The fertilization rate was significantly higher in the human serum albumin group than in the foetal cord group (62.9 versus 53.8%, $P < 0.025$). Implantation rates per transferred embryo were not significantly different but there was a significantly higher pregnancy rate per embryo transfer in the human serum albumin group (45.7 versus 35.9%, $P < 0.05$). The data demonstrated that the use of human serum albumin as a protein supplement in culture medium in human IVF programs is associated with improved embryonic quality and significantly higher pregnancy rates.

Ben-Yosef et al. performed a study comparing two embryo culture systems, Irvine Scientific's P1 Medium and Cook IVF Medium. The media solutions were both supplemented at 20% with Irvine Scientific's Serum Supplement Substitute, a 6% total protein solution containing 84% human serum albumin and 16% human globulins. This product was developed in 1993 and has now been replaced with Dextran Serum Supplement which contains 5% human serum albumin and 2% dextran in normal saline. A prospective randomised study was performed using 349 patients which represented 375 cycles. The fertilisation rates were similar and no differences were found in the morphological characteristics of cultured embryos. The study concluded that a significantly higher proportion of the embryos incubated in the P1 Medium reached the 4-cell stage on day 2 or the 6-cell stage on day 3 post fertilisation compared to the other media.

- Labelling

The Precautions and Warnings Section of the media product leaflet for each of the products in the application informs the end user that the product contains human source material which has been used in the manufacture of the product. It is stated that the donors of the source material have been screened for CJD and that the material has been tested by FDA licensed kits and found to be non reactive to the antibodies, for Hepatitis B surface antigen (HBsAg), antibody to Hepatitis C (HCV) and antibodies to Human Immunodeficiency Virus (HIV). In addition it is noted that no test method can give complete assurance that products derived from human sources are non infectious and recommends handling the products as if it were capable of transmitting infection, using universal precautions. The inclusion of the warning statement is considered to be adequate.

Discussion on Quality, Safety and Usefulness

- Quality

Medicinal product before incorporation in the medical device

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines and Ph. Eur. monograph for human albumin. The information provided in the application showed a consistent batch-to-batch production of Human Albumin L/A 25% achieving an adequate quality for the drug substance and the drug product. The manufacturing process of the drug

substance and drug product were described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications.

The capacity and robustness of the manufacturing process to inactivate and remove viruses has sufficiently been investigated and, in summary, the virus safety of Human Albumin L/A 25% has adequately been demonstrated. No materials of bovine or other TSE-susceptible animal species are used in production. The Human Albumin L/A 25% is produced from human plasma in the USA. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. In addition, investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process.

Medicinal product in the context of its use in the medical device

In general, the quality aspects of the incorporation of Human Albumin as ancillary medicinal substance in the vitro fertilisation media were sufficiently addressed.

The manufacturing process is described and critical steps are performed under sterile conditions. The controls of starting materials are adequate. The manufacturer of the medical device has developed and validated a method to test albumin concentration at the lot release of the media.

The company provided stability data of the solutions to support the stability of the media throughout the shelf life. The measures of the concentration of albumin in samples of each media after the expiration of the media support the stability of it throughout the shelf life of the medical device.

- Safety and Usefulness

Albumin is added to most of IVF culture media because it is widely considered to be of benefit. In the culture media it is thought that albumin has a number of roles, for example as a carrier of growth promoting substances such as fatty acids and vitamins, a nutrient and a membrane stabilizer.

Until the 1990s the most commonly used protein source in media for human IVF was human serum, obtained from the patient herself, human donors or foetal cord. Since then serum has been replaced as a protein source with various preparations of plasma-derived human serum albumin. The replacement of serum with human albumin has been carried out in order to reduce the risks of transmission of viral disease. Albumin is produced after a careful selection and screening of plasma donors and its manufacturing process has been extensively validated for virus inactivation/removing capacity. Nevertheless, it is noted that no test method can give complete assurance that products derived from human sources are not infectious. Therefore the applicant has included a warning statement regarding virus transmission in the Precautions and Warnings section of the product leaflet for each of the media solutions, which is considered adequate.

The Irvine Scientific Reproductive Media Products culture media have been designed for use in ART procedures to mimic the physiological conditions required for storage, manipulation and transfer of gametes, embryos or sperm. In these solutions human albumin, supplied by Talecris Biotherapeutics, functions as an ancillary substance.

The EMEA Document CPMP/PhVWP/BPWG/223/99 rev.2 "Core SPC for Human Albumin Solution" states that:

- 1- Human albumin is a normal constituent of human plasma and acts like physiological albumin
- 2- To date, human albumin has not been reported to be associated with embryo- foetal toxicity, oncogenic or mutagenic potential.
- 3- No signs of acute toxicity have been described in animal models.

Several published clinical studies support the safety and usefulness of Albumin in IVF media solutions.

While the efficacy of the media itself is not being assessed in this report, the materials in the media do not give rise to any concern. The amount of albumin that the patient would be exposed to is considered to be very low. It is also notable that the female genital tract is exposed, physiologically, to much higher amounts of albumin present in the menstrual blood.

3.4. Overall conclusions and recommendation

Quality

The quality of Human Albumin 25% before and after the incorporation in vitro fertilisation media has been sufficiently demonstrated.

The capacity and robustness of the manufacturing process of the Human Albumin 25% to inactivate and remove viruses has been sufficiently investigated. In summary, the virus safety of the Human albumin L/A 25% has been adequately demonstrated. Donors are excluded with respect to (v)CJD risk according to EU- and US-regulations. Investigational studies provided evidence that significant removal of prions can be expected from the manufacturing process of Human Albumin 25%.

The manufacturer has included a test to measure the concentration of the albumin at the batch release of the media and during the shelf life.

Safety

The Note for guidance CPMP/BPWG/BWP/561/03 states that: 'There have been no reports of virus transmission with albumin manufactured to European Pharmacopoeia specifications by established processes', the use of albumin in the Irvine Scientific Media Solutions is different from the normal use. To address this, a report has been provided which details the viral safety measures incorporated into the albumin process. These include donor screening, testing of plasma donors and plasma manufacturing pools, a 60 day hold for donations and the virus clearance validation studies carried out on the albumin manufacturing process.

A report on the relationship between the parvovirus B19 reduction capacity of the albumin manufacturing process and the potential maximum virus load has been provided and the measures taken to minimise the risk of virus transmission are considered adequate.

Usefulness

Albumin is added to most of IVF culture media because it is widely considered to be of benefit. In the culture media it is thought that albumin has a number of roles, for example as a carrier of growth promoting substances such as fatty acids and vitamins, a nutrient and a membrane stabilizer.

The EMEA Document CPMP/PhVWP/BPWG/223/99 rev.2 "Core SPC for Human Albumin Solution" states that:

- 1- Human albumin is a normal constituent of human plasma and acts like physiological albumin
- 2- To date, human albumin has not been reported to be associated with embryo- foetal toxicity, oncogenic or mutagenic potential.
- 3- No signs of acute toxicity have been described in animal models.

The clinical evaluation report submitted by the applicant reviews the literature supporting the usefulness of human albumin in IVF media solutions.

Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality, safety and usefulness of Human Albumin Solution used as ancillary medicinal substance in the "Reproductive Media Products containing Human Tissues/Plasma" manufactured by Irvine Scientific was favourable and therefore granted a positive opinion in the consultation procedure.

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3. Ben-Yosef D, Amit A, Azem F, Schwartz T, Cohen T, Mei-Raz N, Carmon A, Lessing JB, Yaron Y, Prospective randomized comparison of two embryo culture systems: P1 medium by Irvine Scientific and the Cook IVF Medium, Journal of Assisted Reproduction Genetics, 2004Aug; 21(8):291-5.