8 August 2012
EMA/CHMP/100577/2012

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: Cook IVF Cell Culture Media

Ancillary medicinal substance: Human Albumin Solution

EMEA/H/D/2592

Applicant: Det Norske Veritas Certification AS, Norway

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8545
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Administrative information

Invented name of medical device:	Cook IVF Cell Culture Media
INN (or common name) of the ancillary medicinal substance:	Human Albumin Solution
Applicant for medical device CE certification:	William Cook Australia Pty Ltd.
Notified body:	Det Norske Veritas Certification AS, Norway
Applied intended purpose of the device:	In vitro fertilisation for sub-fertile couples. Each individual product within the cell culture media suite serves a purpose in the overall treatment procedure.
Intended purpose of the ancillary medicinal substance in the device:	To assist function of the IVF media. The protein prevents embryos and gametes sticking to the devices used to collect and culture embryos.
Pharmaceutical form(s) and strength(s) of the ancillary medicinal substance:	Human albumin solution 25% Liquid, 4 - 20mg/ml

1. Background information on the procedure

1.1. Submission of the dossier

The notified body Det Norske Veritas Certification AS submitted to the European Medicines Agency (EMA) on 01 June 2011 an application for consultation on Human Serum Albumin as ancillary medicinal substance(s) used in a medical device Cook IVF Cell Culture Media, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

Steps taken for the assessment of the product

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

Rapporteur: Ian Hudson Co-Rapporteur: Patrick Salmon

- The application was received by the EMA on 01 June 2011.
- The procedure started on 22 June 2011.
- The Rapporteur's first assessment report was circulated to all CHMP members on 09 September 2011. The Co-Rapporteur's first assessment report was circulated to all CHMP members on 09 September 2011.
- During the meeting on 17-20 October 2011, the CHMP agreed on the consolidated list of questions to be sent to the applicant. The final consolidated list of questions was sent to the applicant on 20 October 2011.
- The applicant submitted the responses to the CHMP consolidated list of questions on 08 December 2011.
- The Rapporteurs circulated the joint assessment report on the applicant's responses to the list of questions to all CHMP members on 02 February 2011.
- During the meeting on 13-16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the committee, issued a positive opinion for quality and safety including the clinical benefit/risk profile of Human Albumin Solution as ancillary medicinal substance used in Cook IVF Cell Culture Media on 16 February 2012.

1.2. Manufacturers

Manufacturers of the active substance used as ancillary medicinal substance

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Straße 235
AT-1100 Vienna
Austria

Octapharma AB
Elersvägen 55
SE 112 75 Stockholm
Sweden

Inspections of these manufacturing site were carried out by AGES (25-26/03/2009) and MPA (03/09/2009) respectively. The findings of the inspections are in compliance with the Community Good Manufacturing Practice requirements.

Manufacturers responsible for batch release in the European Economic Area

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Straße 235
AT-1100 Vienna
Austria

Octapharma AB
Elersvägen 55
SE 112 75 Stockholm
Sweden

Manufacturer of the medical device

William A. Cook Australia Pty Ltd
95 Brandl Street
Eight Mile Plains QLD 4113
Australia

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.

1.3. Remarks to the notified body

A commitment has been given by the applicant, William A Cook, to introduce an albumin concentration test for finished product release testing and stability testing.

It is understood that DNV will not issue the CE mark prior to implementation of an appropriate albumin concentration test.

2. Scientific overview and discussion

2.1. General information

COOK IVF Cell Culture Media are classified as medical devices according to the Commission Directives 93/42/EEC as amended. Det Norske Veritas Certification AS is consulting the CHMP regarding the quality, safety and clinical benefit/risk profile of the albumin component of Cook IVF Cell Culture Media.

COOK IVF Cell Culture Media are products used for in vitro fertilisation (IVF) and assisted reproductive technologies (ART) including the preparation, cultivation and storage of gametes and embryos. These products contain human albumin (HSA) which acts as an ancillary to the medicinal devices. As albumin source, COOK IVF uses Human Albumin Solution 25%.

About the ancillary medicinal substance.

The Human Albumin Solution 25% used as a component of the IVF media is manufactured by Octapharma. Human Albumin Solution 25% (Albunorm 25%) is prepared from human plasma and is virus-inactivated by fractionation and final container pasteurisation.

Octapharma has EEA Marketing Authorisations for Human Albumin Solution (Proprietary name Albunorm/Octalbin) which is available in 3 strengths (human albumin 5%, 20% and 25%). Only the 25% strength is used for the COOK IVF Cell Culture Media submission. Albunorm 25%/Octalbin 25% is a solution for infusion for intravenous use and complies with Ph. Eur. requirements.

Table: Composition of Human Albumin Solution 25%

Name of Active ingredients	**Quantity**	**Function**
Plasma proteins with at least 96% human albumin	250g per 1000mL	Active ingredients
Name of Excipients		**Function**
Sodium		Osmotic and electrolytic component
N-acetyl-DL-tryptophan		Stabiliser
Caprylic acid		Stabiliser
NaOH or HCl		Buffer component
Water for injections		Solvent

About the medical device.

COOK IVF Cell Culture Media is a mixture of physiologically balanced salt solution and may contain a variety of amino acids, vitamins, some simple nutrients such as glucose, and a source of protein. The IVF cell culture media is designed to provide substrates suitable for the changing metabolic needs of gametes and embryos.

These products contain Human Albumin Solution 25% which acts as an ancillary to the medicinal devices providing a stable liquid environment for the oocytes and embryos outside the human body. The HSA prevents the embryos and gametes sticking to the plastic and glassware used to collect and culture embryos during the IVF process. HSA also acts as a micronutrient and as an absorption moiety for any potential embryo toxins that may be introduced into the device by the user during routine use.

The amount of human albumin is dependent on the type of medium and ranges from 4 g/l to 20 g/l.

2.2. Quality documentation

2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself

Drug substance

Starting material

The starting material for the manufacture of Human Albumin Solution 25% is human plasma. All plasma complies with the current version of the Plasma Master File (PMF). An EMA certificate of compliance (EMEA/H/PMF/000008/05/AU/008) has been issued for Octapharma Pharmazeutika Produktionsges.m.b.H. (Vienna, Austria) dated 17 February 2011.

A letter of confirmation has been provided by the PMF holder to notify the medical device manufacturer, William A Cook Australia Pty Ltd, in case of modification to the PMF or product recalls due to look back procedures.

Manufacture, Specifications, Stability

The applicant submitted all the details regarding the manufacture, specifications and stability of human albumin as active substance under the Drug Product section. Therefore this information can be found in the drug product section.

Drug product

Human Albumin Solution 25% is a solution for infusion, used for intravenous administration. The product is filled in infusion bottles containing 50mL and 100mL. The bottles are closed with bromobutyl rubber stoppers.

The qualitative and quantitative composition is detailed in section 2.1. - General information.

Pharmaceutical development

The manufacturing process of human albumin is based on various modifications to the well established Cohn Oncley process to obtain better recoveries of albumin.

Manufacturers

Human albumin solution 25% is manufactured from the starting material (human plasma pools) up to the finished product at two manufacturing sites, Octapharma Pharmazeutica Produktionsges.m.b.H, Vienna, Austria and Octapharma AB, Stockholm, Sweden. Manufacturing licences and GMP certificates issued by an EU Competent Authority have been provided.

Manufacture

The albumin production process utilized by Octapharma is a combination of technical improvements made on the basic Cohn Method fractionation procedure.

The solution is filtered and may be stored in stainless steel tanks or single use bags.

The production of the finished product consists of sterilizing filtration and aseptic filling into the final container, pasteurization and incubation in the final container.

The description of the manufacturing process, together with the validation data from both manufacturing sites, has been presented. The manufacture and equipment between the two sites have been compared. Process validation and batch data have demonstrated consistency of the

manufacturing processes, with reduction of impurities to low levels. The final product complies with the Ph.Eur. monograph for human albumin solution (01/2010:0255).

The composition and physicochemical properties of intermediate fractions have been extensively studied. The manufacturing process is controlled by adequate in-process testing in all critical steps throughout the process. The test methods have been validated and adequate acceptance criteria established. All excipients are of pharmacopoeial grade (Ph.Eur).

Fraction V has been defined as an intermediate and stability data support has been provided. Fraction V may be exchanged between the manufacturing sites.

Specifications

A set of release and shelf life specifications have been provided. The test methods and the limits have been set in accordance with Ph. Eur. Monograph 01/2010:03255.

Container closure system

The albumin is filled into 70 mL (filing volume 50 mL) and 100 mL bottles. The glass bottles are closed with bromobutyl rubber stoppers and sealed with flip-off caps. Details of suppliers have been given.

Stability

Stability studies have demonstrated that the final product, human albumin solution 25% can be stored for 36 months at +2°C to 25°C, protected from light. The container and stoppers have been verified in stability studies.

Adventitious agents' safety

Non-viral adventitious agents

No starting materials derived from bovine origin are used for the production of Human Albumin Solution 25% from plasma to final product..No materials of bovine or other TSE-susceptible animal species are used in production of albumin 25%.

Human Albumin Solution 25% is produced from human plasma collected in some EU countries. Donors are excluded with respect to vCJD risk according to European Directives and guidelines and US regulations. The exclusion criteria have been described in the Plasma Master File EMEA/H/PMF/000008/05/AU/005 and have been considered adequate and in line with current guidance (CHMP Position Statement, CPMP/BWP/2879/02).

In accordance to the Guideline on the investigation of manufacturing processes for plasma derived medicinal products with regard to vCJD risk (CPMP/BWP/5136/03), the capacity of the manufacturing process to remove prions has been validated.

The ability of the manufacturing process to remove TSE infectivity has been adequately demonstrated.

Viral adventitious agents

Starting material for the manufacture of Albumin is human plasma. All donations used by Octapharma comply with the requirements. Each plasma pool is tested and must be non-reactive for viral marker testing according to EC-Note for Guidance III/5193/94. All plasma donations used are tested for HIV, HBV, HCV, HAV and B19V by the collection centres or the Octapharma Group. The testing methods and validation reports are given.

The viral safety of Albumin with regard to enveloped as well as non-enveloped viruses is based on two separate steps with different mode of action.

The viral validation studies were performed with appropriate intermediates from production batches, from both manufacturing sites.

During the procedure the applicant reconfirmed that the plasma used for Human serum Albumin undergoes NAT testing for B19V. After taking into account worst case scenario the estimated number of virus particles per 100 mL vial of Human Serum Albumin 25% is
≤-1.4 log IU B19V. The risk assessment demonstrates an acceptable safety margin regarding B19V for the IVF procedure (≤-5.1 log IU B19V).

The viral safety of Human Serum Albumin 25% has been satisfactorily demonstrated.

2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device

Qualitative and Quantitative particular of the constituents

COOK IVF Cell Culture Media is a mixture of physiologically balanced salt solutions and may contain a variety of amino acids, vitamins, some simple nutrients such as glucose, and a source of protein.

These products contain Human Albumin Solution 25% which acts as an ancillary medical substance.

The products are presented as a liquid formulation, filtered under aseptic conditions and ready for use. Cook IVF media products are packaged in borosilicate glass vials, closed with Fluorotec stoppers and held in place with a tamper-evident seal and polypropylene disc. Package sizes are 3.5, 10, 20, 50, 100 and 250mL.

Description of method of manufacture

The Human Albumin Solution 25% is diluted to 10% with purified water, filtered and concentrated to 20% prior to incorporation in the IVF media. The filtration process is performed to concentrate and purify the albumin.

Control of starting materials

The majority of the starting materials for the Cell Culture Media are of British Pharmacopoeia (BP) quality, with the exception of gentamicin sulphate (Ph. Eur.) and non-pharmacopoeial reagents sodium pyruvate, HEPES (free acid), L-alanyl-L-glutamine, silane coated silica particles, ethylene glycol and trehalose.

The certificates of Analysis (COA) for the starting materials and certificates of origin have been obtained for all relevant raw materials.

One of the solutions of the COOK IVF Cell Culture Media (COOK Sydney IVF Hyaluronidase) contains Hyaluronidase. It has been confirmed that only hyaluronidase sourced from ovine testes is used in the manufacturing process for IVF media and a EDQM TSE certificate of suitability has been provided.

Medical device COOK IVF media

The release tests are performed in-house, and have been qualified, as appropriate, for their intended use. Batch release data for three consecutive lots of IVF media confirms the consistency of manufacturing and compliance with the specifications.

Stability

Octapharma albumin (human) 25% has a recommended shelf life of 3 years for albumin 25% when stored at 2 - 25°C. The report includes data to support a deviation from the recommended storage condition of 37°C for up to 5 days. Confirmation has been provided that the expiry dates of the albumin will not precede the expiry dates of the IVF media.

COOK IVF Media have a shelf life of 20 weeks (unopened) when stored between 2°C and 8°C. The COOK IVF Media are single use only and the unused solution must be discarded after use.

2.2.3. Discussion and conclusion on chemical, pharmaceutical and biological aspects

The COOK IVF Cell Culture Media is manufactured using a 25% Human Albumin Solution manufactured by Octapharma (ancillary medicinal substance) and a mixture of physiologically balanced salt solutions which may contain amino acids, vitamins and glucose.

Octapharma's Human Albumin Solution 25% solution is approved for marketing as a medicinal product in a number of member states in Europe (as Albunorm 25%/Octalbin 25%) and meets the requirements of the Ph. Eur monograph on Human Albumin Solution (Ph. Eur. 2010:0255).

The selection and screening of donors for the plasma used to manufacture human albumin are described in the Octapharma PMF and are in accordance with current requirements. Details of the pharmaceutical grade albumin have been provided, demonstrating a consistent product suitable for use as an ancillary medicinal product.

Safety of the human albumin has been assured by a combination of the EMA PMF, in-process controls and QC release testing for the manufacturing of Albumin 25%, capacity of the manufacturing process for viral reduction/inactivation and potential prion reduction studies, and official release by an OMCL. In addition, a risk assessment based on the use of a total of 5mg albumin during an IVF procedure has been provided for B19 virus, which demonstrates an acceptable safety margin.

The Human Serum Albumin 25% is filtered prior to incorporation in the IVF media. Adequate in process controls have been established to ensure the maintenance of the quality of the albumin. The filtration, aseptic fill and production processes are satisfactorily validated and controlled.

The manufacturing process of the different COOK IVF Media has been adequately described. Acceptable in-process control testing has been established to ensure a quality control of albumin during manufacture. The quality of the IVF media is assured using a number of analytical tests. The MEA is performed as a final control test on all batches of COOK IVF Media products and provides qualitative evidence of the function of the HSA incorporated into the media. Batch release data confirms the consistency of manufacture and compliance with the specifications. It was noted that a test for albumin concentration is not included in the release and stability testing of the media and the applicant committed to introduce a test prior to CE mark.

Stability studies to investigate the HSA within the COOK IVF Media shows data supporting the stability of the HSA within the formulated IVF products during the shelf life. Confirmation has been provided that the expiry dates of the albumin will not precede the expiry dates of the IVF media.

2.3. Non-clinical documentation

Pharmacodynamics

The intended use for this product is to provide a stable liquid environment for oocytes and embryos outside the human body to permit in vitro fertilisation prior to implantation of a fertilised egg. The

purpose of including human serum albumin, at 4-20 mg/ml, in media is to prevent adherence of gametes and embryos to plastic and glassware used in vitro culture. There is no other intended pharmacological effect. The human serum albumin used is that made by Octapharma which is approved as a medicinal product in the European Union. This use of human serum albumin is not novel and other products used for this purpose either include human serum albumin or direct the physician to add human serum albumin prior to use. Earlier experience indicated that using human serum was not as beneficial as human serum albumin.

Pharmacokinetics

No pharmacokinetic studies have been done. This is acceptable as the media is not absorbed by the body.

Toxicity

In vivo exposure is likely to be miniscule in comparison with intravenous use of human serum albumin, where grammes of product can be given intravenously and the applicant estimated that the amount of material that could be exposed when the fertilised egg is transplanted is in the microgramme range. Therefore, systemic toxicity in the recipient female is not conceived as a credible risk. As regards the effect of the albumin on the conceptus, the applicant refers to the history of use of human serum albumin in human embryo culture from which no specific risk is identified and on risk-benefit considerations, proposes that its use is acceptable.

Notwithstanding the foregoing, the applicant supplied data from in vitro tests on the safety of three media, these being K-SIBM, K-SIFM and K-SISM, (Sydney In Vitro Fertilisation Blast media, Sydney In vitro Fertilisation Fertilisation media and Sydney In vitro Fertilisation Sperm media). These were chosen as they represent the media with the most complex mix of chemical constituents. These media have the potential to be in contact with the patient. Testing comprised assessment of sensitisation, cytotoxicity, irritation and genotoxicity. Results suggested no toxic potential. However, all these tests were done with human serum albumin from a source different to that intended to be used in this product and the specific material used was not identified in the material the applicant submitted. Additional testing was done with Cook IVF Media containing human serum albumin sourced from Octapharma. In bacterial reverse mutation testing and in a mouse bone marrow micronucleus test with intraperitoneal injection, results with Blastocyst medium were both negative.

Local tolerance

Vaginal irritation testing and sensitisation testing in guinea pigs were done with Cook IVF media containing human serum albumin sourced from Octapharma. No evidence of irritancy or sensitisation was suggested and the applicant concludes that local tolerability is adequately demonstrated.

2.3.1. Discussion and conclusion on the non-clinical documentation

The applicant's summary of pharmacodynamics is sufficient for this application and the absence of pharmacokinetics can be agreed given the nature of likely exposure. The relevance of genotoxicity testing is limited for this product as there is no expectation that the active principles penetrate the cell. Nevertheless, the testing conducted gave, as expected, negative results. As local effects may occur at transplant of a fertilised egg, the applicant conducted testing which showed no vaginal irritancy or sensitisation potential. There is no expectation of systemic toxicity, given the very limited exposure and the experience from use of much greater doses given intravenously in other areas of medicine. Effects on the fertilised egg are concluded to be favourable. In conclusion, non-clinical considerations are sufficient to support a positive recommendation.

2.4. Clinical evaluation

2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body

Det Norske Veritas as Notified Body has assessed and verified the design dossiers and the technical file for the Cook IVF Cell Culture Media medical device as well as the different production steps with the focus on the usefulness of Human Serum Albumin.

According to the Notified body, Human Serum Albumin is not a new product. It has been on the market and in use for decades. There exist already CE marked IVF Media on the market today using human serum albumin.

The intended use for the Cook IVF Cell Culture Media is to provide an external liquid environment for cell growth for the use in human in-vitro fertilization techniques, which is the same as for other CE marked devices. Albumin is the predominant form of protein found in human fallopian tube secretions. The presence of protein prevents embryos and gametes "sticking" to the devices used to collect and culture embryos. Human serum albumin is needed for sperm capacitation and the fertilisation process. The HSA in the Cook IVF Cell Culture Media has an ancillary effect. The purpose is to assist the function of the medical device, and the HSA is not intended to have any medicinal / pharmacological effect.

With reference to MEDDEV 2.1/3 rev 3, section C3, CHMP acknowledges that Human Serum Albumin is a well-known medicinal substance used for the current purpose and that aspects of usefulness may be addressed by experience, as described by the Notified Body.

In addition, the applicant has submitted a clinical evidence report (CEA25034 v1) that summarises clinical data using the current product and complaint reports received on the current product. The Media Suite has been in commercial production since 1997; the current formulation has been commercially available since 2008. The applicant claims comparable efficacy results to those published by the Australian Institute of Health and Welfare National Perinatal Statistics Unit. The applicant refers to 44 complaints on product efficacy from over 600,000 products distributed in years 2007-2010 inclusive; no action was taken after review because of the low numbers and because of the inability to determine the role of the current product in the complaints of efficacy.

The usefulness of the currently proposed Human Serum Albumin, as described, may be accepted.

2.4.2. Clinical safety of the medical device

The notifed body is of the view that although recombinant albumin has become commercially available, some safety concerns still exist for its clinical use as the protein is produced in a non-mammalian cell line. This could potentially lead to non-mammalian peptide impurities being introduced into patients and exposure of the embryo to foreign peptides. Recombinant albumin that is not exposed to human blood may be deficient of essential peptides that bind to the many sites found in / on the albumin molecule. If these sites are empty they may act as a "sponge" and bind essential autocrine molecules produced by the embryo that are otherwise required for normal development. Consequently, the notified body notes that the risk associated with the use of recombinant albumin could represent significant developmental challenges to embryos when such a product is used as a replacement for human serum albumin.

Human Serum Albumin is not a new product. It has been on the market and in use for decades. The production and use of Human Serum Albumin are under strict regulations, and should ensure a high degree of safety.

The Human Serum Albumin in the Cook IVF Media Suite is purchased from an established manufacturer: Octapharma (sites in Sweden & Austria). Octapharma has obtained a plasma master file certificate from the EMA. Octapharma has given the manufacturer of the Cook IVF Media Suite and the Notified Body full access to both the Plasma Master File and the Product Master File. Octapharma has committed to report to the manufacturer William Cook Australia Pty Ltd eventual recalls or vigilance cases and if any changes are made to their plasma master file or Human Serum Albumin product.

According to the notified body, William Cook Australia Pty Ltd is EN IS0 13485:2003/ AC:2007, IS0 13485:2003 certified by TUV SUD product service. This standard is harmonised with the Medical Device Directive 93/42/EC and ensures control of all steps related to design, production and sales as well as post marketing surveillance of medical devices. Traceability is a key point in this and applies from the staring material to finished product. The quality management system standard imply periodical audits at the manufacturer and this has been performed annually by TUV SUD. The essential requirements according to the medical devices directive have been assessed and verified by Det Norske Veritas.

The device is to be used on a relatively limited number of patients and in limited number of procedures on each patient. The IVF Media Suite is for in vitro use but the possibility that some small portion of the device will be implanted with the fertilised egg is present. This risk is mitigated by choosing a pharmaceutical grade of Human Serum Albumin, appropriate biocompatibility and embryo safety testing.

With reference to MEDDEV 2.1/3 rev 3, section C3, CHMP acknowledges that Human Serum Albumin is a well-known medicinal substance used for the current purpose; aspects of safety may be addressed by experience, as described by the Notified Body.

In addition, the applicant refers to commercial records for years Jan 2007 to Dec 2010: A post-marketing surveillance procedure is in operation. Over 600,000 products were distributed; 282 complaints were made on shipping and packaging; 102 complaints were made on product appearance and contamination. These issues did not lead to any issue of clinical significance. The applicant states that complaints are regularly reviewed and that there were not any clinically-relevant complaints that resulted in corrective action.

The source of human serum albumin has changed from other manufacturers to Octapharma (pending CE approval). Argument submitted by the applicant (based on regulatory approval of the source human serum albumin and Quality control systems) may be accepted as justification that it is possible to change human serum albumin in the media without affecting the quality, safety and effectiveness of the media.

The clinical safety of the currently proposed medical device, as described, may be accepted.

Post-marketing surveillance of the device is governed by medical device regulation and is not within the remit of the European Medicines Agency.

2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device

According to the medical device manufacturer, the risk posed to the mother by the IVF solutions is extremely low. The major risks are sensitivity to any of the ingredients, especially gentamicin and Human Serum Albumin, and the inherent risk involved with the use of any blood derived product. The risk analysis highlighted that the Human Serum Albumin poses the greatest risk to the patient and the embryo. The Human Serum Albumin has appropriate donor selection and is processed to mitigate the

risk of viral, microbial and prion disease transmission. The controls exerted by COOK on the manufacture of the media suite results in a consistent and reproducible high quality product.
The notified body is of the view that the device is to be used on a relatively limited number of patients and in limited number of procedures on each patient. The IVF Media Suite is for in vitro use but the possibility that some small portion of the device will be implanted with the fertilised egg is present. This risk is mitigated by choosing a pharmaceutical grade of Human Serum Albumin, appropriate biocompatibility and embryo safety testing.
The CHMP acknowledges that the clinical benefit derives from successful pregnancy leading to a live birth. There is risk associated with using a blood-derived product, as described; there are procedures in place to minimise risk, as described by the applicant and confirmed by the Notified Body.

The clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device may be considered to be positive.

2.4.4. Discussion and conclusion on the clinical evaluation

It is confirmed that Det Norske Veritas Certification AS, Norway is a Notified Body that appears on the NANDO website as NB 0434 and is designated to carry out conformity assessments of medical devices according to EU Directive 93/42/EEC, as amended.
It is confirmed that the currently proposed Human Serum Albumin was the product involved in a successfully completed Decentralised European Procedure: Human Albumin Solution 25%, 250 g/L; licensed to Octapharma Ltd; EU procedure number DE/H/480/004/DC; CMS = AT, RO, FI, SE, FR, HU, NO, IT, CY, EE & UK; completed May 2010.
The Notified Body has submitted a clinical evaluation that refers to many years experience of Human Serum Albumin in IVF products that are already licensed and on the EU market.
It is acknowledged that (i) Human Serum Albumin is a well-known substance as used in IVF cell media and that (ii) the currently proposed Human Serum Albumin is produced by an EMA-certified manufacturer (Octapharma Ltd.).
The source of human serum albumin has changed from other manufacturers to Octapharma (pending CE approval). Argument submitted by the applicant (based on regulatory approval of the source human serum albumin and Quality control systems) may be accepted as justification that it is possible to change human serum albumin in the media without affecting the quality, safety and effectiveness of the media.
The clinical evaluation of usefulness and risk/benefit of the currently proposed Human Serum Albumin and clinical safety of the proposed medical device, as described, may be accepted.

2.5. Overall conclusions on the quality and safety including the clinical benefit/risk profile of the ancillary medicinal substance in the context of its use in the medical device

From a quality, non-clinical and clinical perspective, the overall benefit/risk assessment is considered to be positive.

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus that the quality and safety including the benefit risk profile of Human Albumin solution 25% used as ancillary medicinal substance(s) in the Cook IVF Cell Culture Media was favourable and therefore granted a positive opinion in the consultation procedure.