14 November 2024
EMA/22987/2025
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: VitaVitro Vitrification Kit, VitaVitro Warming Kit

Ancillary medicinal substance: human albumin solution

Procedure No. EMEA/H/D/006410/0000

Note

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

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List of abbreviations

- ART: Assisted Reproductive Technology
- CE: Conformité Européenne (European Conformity)
- CHMP: Committee for Medicinal Products for Human Use
- DP: Drug Product
- EMA: European Medicines Agency
- EMEA: European Medicines Agency
- GCP: Good Clinical Practice
- GMP: Good Manufacturing Practice
- HHM: Human Holding Medium
- HSA: Human Serum Albumin
- HV1: Human Vitrification Solution 1
- HV2: Human Vitrification Solution 2
- HW1: Human Warming Solution 1
- HW2: Human Warming Solution 2
- INN: International Non-proprietary Name
- IVF: In Vitro Fertilisation
- MDR: Medical Device Regulation
- NAT: Nucleic Acid Testing
- OMCL: Official Medicines Control Laboratory
- Ph.Eur.: European Pharmacopoeia
- PMF: Plasma Master File

1. Background information on the procedure

1.1. Submission of the dossier

The notified body BSI Group - The Netherlands BV, on behalf of the device manufacturer Shenzhen Vitavitro Biotech Co. Ltd., submitted to the European Medicines Agency (EMA) on 11 October 2023 an application for consultation on human albumin solution incorporated as an ancillary medicinal substance(s) in the medical device VitaVitro Vitrification Kit, VitaVitro Warming Kit, in accordance with the procedure falling within the scope of Directive 93/42/EEC, as amended.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

Co-Rapporteur: Fatima Ventura

The application was received by the EMA on	11 October 2023
The procedure started on	1 February 2024
The Rapporteur's first assessment report was circulated to all CHMP members on	22 April 2024
The Co-Rapporteur's first assessment report was circulated to all CHMP members on	07 May 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	05 August 2024
The Rapporteurs circulated the joint assessment report on the responses to the List of Questions to all CHMP members on	23 September 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 October 2024
The Rapporteurs circulated the joint assessment report on the responses to the list of outstanding issues to all CHMP members on	30 0ctober 2024
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 an ancillary medicinal substance(s) used in VitaVitro Vitrification Kit, VitaVitro Warming Kit on	14 November 2024

1.3. Manufacturers

1.3.1. Manufacturer(s) of the active substance used as ancillary medicinal substance

Instituto Grifols, S.A.

Poligono Ind. Levante

c/Can Guasc 2

Parets del Valles

08150 Barcelona

SPAIN

1.3.2. Manufacturer(s) of the finished product used as ancillary medicinal substance

-

1.3.3. Manufacturer(s) responsible for batch release

Instituto Grifols, S.A.

Poligono Ind. Levante

c/Can Guasc 2

Parets del Valles

08150 Barcelona

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

Not applicable.

1.3.5. Manufacturer(s) of the medical device

Shenzhen Vitavitro Biotech Co. Ltd.
601 Building B Haikexing Strategic Emerging Industrial Park
No. 16 Baoshan Road
Pingshan District
518118 Shenzhen
CHINA

1.4. Recommended measures to the notified body

As discussed at CHMP, it would be recommended that the notified body request the following from the medical device manufacturer for device approval:

Area	Description
Labelling	The product labelling should contain information with regards to the risks of albumin used within these media, in particular the risk of transmissible infections, which is low but not non-existent.

2. Scientific overview and discussion

2.1. General information

The notified body BSI Group, on behalf of the device manufacturer, submitted to the European Medicines Agency (EMA) on 11 October 2023 an application for consultation on human serum albumin (HSA), as an ancillary human blood derivative used in the medical device VitaVitro Vitrification Kit, VitaVitro Warming Kit, in accordance with the procedure falling within the scope of Regulation (EU) 2017/745.

VitaVitro Vitrification Kit is used for vitrification of human MII-phase oocytes and embryos for assisted reproductive technology (ART). This kit is designed for use with Vitavitro Warming Kit. Vitavitro Warming Kit is intended for the warming of human MII-phase oocytes and embryos that have undergone vitrification using Vitavitro Vitrification Kit for ART procedures.

Vitrification is an alternative approach to cryopreservation that enables hydrated living cells to be cooled to cryogenic temperatures in the absence of ice rapidly. The buffer system maintains the pH value of the media. Cryoprotectants act primarily by reducing the amount of ice that is formed at any given sub-zero temperature.

In the medical device, the human albumin solution functions chemically as a buffer and a molecular carrier. Principally, it also enables handling of the oocytes and embryos, which otherwise can easily stick to plastic dishes.

VitaVitro Vitrification Kit device contains three component media:

- Human holding medium (HHM)
- Human vitrification solution 1 (HV1)
- Human vitrification solution 2 (HV2)

VitaVitro Warming Kit device contains three component media:

- Human holding medium (HHM)
- Human warming solution 1 (HW1)
- Human warming solution 2 (HW2)

2.2. Quality documentation

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

The ancillary human blood derivate subject to this consultation is a human albumin solution, referred to also in the dossier submitted as human albumin drug product (HADP) or Human Albumin Grifols. During the assessment, it was clarified that the Human Albumin Grifols 20% (Albutein) has marketing authorisations in the EU and it was also confirmed that all albumin batches used for manufacture of VitaVitro will have an OCABR batch release certificate issued by an Official Medicines Control Laboratory (OMCL).

Human Albumin Grifols 20% (Albutein) manufactured by Grifols is used as the source of albumin.

The albumin is manufactured from human plasma derived from appropriately screened donor pools and processed for the removal/inactivation of transmissible agents. The plasma starting material is subject to the authorised EMA plasma master file (PMF) certification procedure – EMEA/H/PMF/000002/04/AU/039/G issued on 9 November 2023.

2.2.1.1. Active substance

The active substance (AS) section only relates to the human plasma.

Information regarding the manufacture and control of the albumin medicinal product is included in the finished product section. Reference is also made to the PMF EMEA/H/PMF/000002/04/AU/039/G for the human albumin by Instituto Grifols, and the PMF dossier as well as the certification report are provided.

2.2.1.2. Finished product

2.2.1.2.1. Description of the product and pharmaceutical development

Composition

The finished product (FP) is a human albumin solution that contains sodium chloride, sodium caprylate (sodium octanoate), sodium acetyltryptophan and water for injections. All excipients comply with the European Pharmacopeia (Ph.Eur). The composition is acceptably described.

Pharmaceutical development

Information on pharmaceutical development was not submitted. However, as the human albumin used is a medicinal product approved in EU - Human Albumin Grifols 20% (Albutein) is approved in several EU countries through mutual recognition procedure (MRP), this information is approved and included in the marketing authorisation (MA) dossier for the EU-approved albumin product. This can be considered acceptable.

2.2.1.2.2. Manufacture of the product and process controls

Instituto Grifols, S.A., C/Can Guasch 2 Poligono Industrial Levante, 08150 Parets del Vallés (Barcelona), Spain, is responsible for the manufacturing process and batch release of the finished product.

Manufacture

A summary flowchart of the manufacturing process has been provided.

The starting material used to manufacture Human Albumin Grifols 20% is human plasma which complies with the requirements set forth by the European Community concerning its origin, control as well as storage and transport conditions.

The manufacturing process is based on the modified Cohn method: Once thawed, the plasma is mixed to obtain the starting pool. Fractionation is accomplished through a series of cold ethanol precipitation reactions carried out under varying ethanol concentrations, pH ranges, ionic strengths and temperatures removing blood proteins in fractions I, II+III, IV1+ IV4, while albumin remains in solution up to the final precipitation into the Fraction V of the Cohn method.

Fraction V is resuspended, clarified, concentrated and further subjected to a diafiltration process. Then, the stabilisers sodium caprylate and N-acetyltryptophan are added to the albumin solution and the resulting bulk solution is subjected to a heating process. This albumin solution is further concentrated, adjusted the final concentration of NaCl and sodium caprylate and N-acetyltryptophan as final excipients, and sterile filtered, to obtain the final sterile bulk.

Formulated bulk is sterile filtered and aseptically filled into sterile final containers, and then the final containers are subjected to a process step to inactivate any possible viruses that might be in the solution.

After a quarantine period, 100% of the vials are subjected to a final visual inspection and packaging.

Although a full quality Module 3 for the human albumin has not been provided, all plasma used for the manufacture complies with the current version of the approved plasma master file (PMF). The PMF certificate no: EMEA/H/PMF/000002/04/AU/039/G issued on 9 November 2023 has been provided.

The applicant has also confirmed that human albumin solution used as an ancillary substance in Vitavitro has a marketing authorisation in the EU and therefore the process is approved in the EU for this product.

The information on the manufacturing process is acceptable and in compliance with the requirements of the Guideline on plasma-derived medicinal products.

2.2.1.2.3. Control of excipients

The excipients are sodium chloride, sodium caprylate (sodium octanoate), sodium N acetyltryptophanate and water for injections. Since the specifications for all excipients comply with Ph.Eur., no further information is needed.

2.2.1.2.4. Product specifications

Human Albumin Grifols 20% complies with the European Pharmacopoeia monograph “Human Albumin Solution” and will always be adapted to the edition in force. Final product specifications for Human Albumin Grifols 20% are provided.

The finished product (FP) specification complies with requirements in the Ph.Eur. monograph for human albumin solution and most of the test methods are performed in accordance with Ph.Eur. Information is approved and included in the marketing authorisation (MA) dossier for the EU-approved albumin product. This can be considered acceptable.

A thorough risk assessment was conducted for the replacement of rabbit pyrogen testing by the LAL test. The justification for the use of bacterial endotoxin test for the control of pyrogens is found acceptable.

Certificate of analyses has been provided for three batches demonstrating results well within specification criteria.

Information on nitrosamine risk evaluation performed by the manufacture of the human albumin has been provided. This evaluation was performed in line with EMA/409815/2020, and it is concluded in the report that for the product human albumin no risk of presence of N-nitrosamines was identified. The information provided is found sufficient.

2.2.1.2.5. Container closure system

Detailed information regarding the container closure system has been provided. For the primary packaging (vial and stopper) compliance with Ph. Eur. requirements has been confirmed.

2.2.1.2.6. Stability of the product

The claimed shelf-life for Human Albumin Grifols 20% 50 ml and 100 ml product is 3 years, between 2ºC and 30ºC.

The reports from studies performed by Grifols have been provided. Both real time studies at 5ºC and 30ºC have been performed as well as accelerated studies at 40ºC. It is concluded by Grifols that data obtained supports a storage period of 3 years at temperatures between 2°C and 30ºC. This is agreed to, and the proposed shelf life is found acceptably justified.

2.2.1.2.7. Adventitious agents

A short virus risk assessment has been provided describing measures taken to minimise risk of virus transmission. This includes selection and testing of donors, testing of mini pool and fractionation pools for viral markers. The applicant states that the EU PMF (PMF EMEA/H/PMF/000002/04) applies for Human Albumin Grifols.

In the virus risk assessment, it is stated that plasma donations are analysed by NAT in mini pools for HIV, HBV, HCV, HAV and B19V. Some information was found not to be in line with information provided in the Grifols EU PMF and therefore not accepted. The applicant was asked to provide confirmation that mini-pool and/or manufacturing pool testing for Parvo B19V by NAT is in place for all albumin batches used in IVF solutions, to ensure an adequate safety margin

Since this albumin is to be used in IVF media, special care should be taken regarding parvo B19 and calculation of the safety margin for this virus is required.

Virus clearance studies were performed, and a summary of results is presented.

A very short summary of the results from virus clearance studies has been provided. The results are as expected for albumin products manufactured by fractionation process and pasteurised in final container. Since it has been confirmed that this Human Albumin 20% Grifols is approved in an EU member state, this level of information can be accepted.

In the response to the Day 180 list of outstanding issues (LoOI), the remaining issue on the safety margin for B19V was not found to be acceptably addressed. However, before CHMP opinion an updated risk assessment was provided by the albumin manufacturer Grifols. The remaining issue in relation to the safety margin for B19V was consequently found resolved.

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

2.2.2.1. Qualitative and quantitative particular of the constituents

The ancillary human blood derivative (human albumin solution) is supplemented into both devices with a concentration of 6%. The concentration of the active ingredient (Albumin) is 12 mg/ml in the final devices. Both devices are liquid, and the albumin presents as free ingredient. The ancillary human blood derivative (human albumin solution) is not modified during its incorporation into the medical device.

The complete qualitative and quantitative composition of all solutions in VitaVitro Vitrification Kit and VitaVitro Warming Kit has been provided. The information is found acceptable.

2.2.2.2. Description of method of manufacture

The manufacturing processes of both devices are identical which is in sequence consisted of:

Weighting the compositions → Configuring liquid (compounding all compositions in water) → Ultrafiltration (filtration sterilisation) and Filling (dispensing the product into the primary packaging vial) → Sealing (covering the cap of vial) → Final product. The HSA is used as received and will be added directly together with other compositions to obtain the final HSA concentration (12 mg/mL). The manufacturing process has been described in sufficient detail.

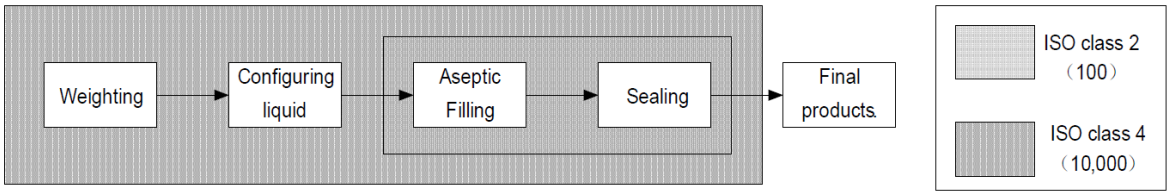

Figure 1. Manufacturing process of VitaVitro Vitrification Kit and Warming Kit

2.2.2.3. Control of starting materials

The raw materials will be inspected as per the incoming inspection procedures before they are put in storage. The inspection items are listed.

After request, this section has been updated to include more information, or clear references to documents where this information can be found in the dossier.

Information has been provided on contract between the albumin manufacturer and VitaVitro, including information on traceability from blood/plasma donations through to HSA all the way to the medical device batch and vice versa. It has also been confirmed that there are systems in place to ensure that the HSA would not expire during the shelf life of the devices.

After request, it has been confirmed that an OCABR certificate is required for each batch of HSA used for the manufacture of the VitaVitro devices. This is to comply with the requirements by section 6 of Annex IX to Regulation (EU) 2017/745.

The controls of incoming albumin have been stated and the method used for the control of the content of incoming albumin is found suitable and acceptable for its purpose.

2.2.2.4. Control test carried out at intermediate stages of the manufacturing process of the medical device

Tests are performed for endotoxin, osmolality, pH and bioburden. No test for albumin content is performed as in-process test. This can be accepted considering that tests for albumin is performed on the final container of the medical device.

2.2.2.5. Final control tests of the ancillary medicinal substance or the ancillary human blood derivative in the medical device.

The final inspections profile of the device is listed.

In the initial application, no test for albumin content was included in the specification for the final container. This has been revised and a test for albumin content has now been included. Summaries of the method description and method validation has been provided. The information is found acceptable and the HPLC method used acceptably validated.

2.2.2.6. Stability

The shelf life of VitaVitro Vitrification Kit and Warming Kit when stored between 2ºC and 8ºC is twelve (12) months for both products.

A package qualification and shelf-life study were conducted to provide documented evidence that the packaging for the device maintains a sterile barrier and protects the functional integrity of the device following simulated transportation conditions and real time aging for twelve (12) months. Detailed data from respective parameter has been presented in this report. All parameters met the acceptance criteria after 13 months of storage.

The stability data initially presented did not include a specific test for albumin. In the response, the Company explained that the content of HSA has been tested during the shelf-life verification of the two devices and the

results of HSA content have been added to the updated report of the two devices. The new stability data shows that the albumin content is stable for up to 13 months. The data provided is acceptable.

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

Although a full quality Module 3 for the human albumin has not been provided, all plasma used complies with the current version of the approved plasma master file (PMF). The applicant has also confirmed that human albumin product used as an ancillary substance in Vitavitro has a marketing authorisation in the EU and the information is approved and included in the MA dossier for the EU approved albumin product.

The major objection raised in the Day 120 LoQ related to the missing information on nitrosamines risk evaluation, has been acceptably resolved. It has been clarified that the Albumin Grifols is an EU approved medicinal product within several EU countries and also confirmed that all albumin batches used for manufacture of VitaVitro will have an EU OCABR certificate, as required by section 6 of Annex IX to Regulation (EU) 2017/745.

One of the issues remained at Day 180, requesting a revised virus risk assessment in relation to parvo B19. The initial virus risk assessment provided in the dossier was questioned since its basis, in relation to B19V NAT testing, was found to be not in line with the information contained in the Grifols PMF. The response to the Day 180 question was not found acceptable and therefore the issue raised in relation to the virus risk assessment, to ensure an adequate safety margin for B19V taking into account the use of albumin in IVF solutions, was not solved. However, before CHMP opinion an updated risk assessment was provided by the albumin manufacturer Grifols and the remaining issue in relation to the safety margin for B19V was consequently found resolved.

The closing sequence will include the information provided on this topic and minor amendments.

2.3. Non-clinical documentation

The Application concerns the usefulness and safety of the ancillary substance HSA in the VitaVitro vitrification kit and the VitaVitro warming kit manufactured by Instituto Grifols, S.A., The applicant has briefly described the rational for incorporating HSA as an ancillary human blood derivative in the VitaVitro Vitrification Kit and VitaVitro Warming Kit. No Pharmacokinetics studies have been performed with HSA, which is considered acceptable. The product is not intended for direct administration to the patient, and any potential exposure of HSA from the VitaVitro kits will be minimal and of no pharmacokinetic relevance.

The Applicant has not performed any general toxicology studies or other standard toxicity studies to evaluate the toxicity of HSA. This is considered acceptable since the VitaVitro solutions are not intended to come into direct contact with the uterus mucosal membrane, why the exposure can be considered negligible.

The Guideline on Core SmPC for Human Albumin Solution (EMA/CHMP/BPWP/494462/2011 rev.3) comprehensively evaluates the toxicity aspects of human albumin. As a natural component of human plasma, human albumin mimics physiological albumin functions. Single-dose animal studies have shown minimal relevance, with no signs of acute toxicity observed, making it challenging to determine toxic or lethal doses or dose-response relationships. Repeated dose toxicity studies are not feasible due to the development of antibodies against the foreign protein in animal models. Importantly, human albumin has not been linked to embryo-fetal toxicity, oncogenic effects, or mutagenic potential.

That said, bacterial endotoxin in IVF culture media is a known potential cause of reduced success in IVF treatment with fewer ova fertilised, poorer quality of fertilised ova, and lower pregnancy rate. There is also a risk of a pyrogenic response in the mother. This risk can be minimised by adding an antibacterial agent to the solution and can be regarded mostly as a quality attribute of the solution. Further, a maternal parvovirus infection can negatively impact implantation and potentially lead to malformations. Although these aspects have not been addressed in the non-clinical section, in the context of IVF the risk is considered minimal.

A number of biocompatibility studies in accordance with ISO 10993-1 2018 have been performed with VitaVitro Vitrification Kit and VitaVitro Warming Kit. The genotoxicity, *In vitro* cytotoxicity, Skin sensitisation and vaginal irritation studies have been performed by Shandong Quality Inspection Center for Medical Device. While having a Chinese Accreditation certificate according to ISO/IEC 17025:2017, the studies have not been performed in accordance with GLP. However, GLP is not a formal regulatory requirement for medical devices. Therefore, this does not raise further concerns.

Regarding the *in vitro* mouse embryo assay, the performing lab (Embryotech Laboratories Inc.) seems to have a GLP accreditation. However, it is not clear if the study has been performed in accordance with GLP. As there is no GLP statement in the study report, the study is considered non-GLP. All the tests fulfilled the acceptance criteria for a passing grade, therefore the conclusion is that the VitaVitro kits meet the requirements of the 10993-1 guideline.

The Applicant has also performed an animal study to evaluate the efficacy and safety of the VitaVitro vitrification and warming kit. The study has been performed by Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences (GIBH). The study has not been performed in accordance with GLP, and while it is assumed that some sort of quality assurance system has been used, nothing has been mentioned in the report regarding regulatory compliance.

The study has evaluated the effects on *in vitro* embryo cleavage and blastocyst formation after cryopreservation and warming, the effects on blastocyst formation in vitrified 8-cell embryos were fertilised *in vivo* and then cultured *in vitro*, and the effects on embryo implantation and post-implantation development after 2-cell embryo transfer. In all studies, the effects on oocytes and embryos were compared after cryopreservation and warming with the VitaVitro kit, the vitrification and thawing kit of Kitazato and with fresh oocytes and embryos. While no statistical differences were identified, it seems as if the fresh oocytes and embryos showed slightly increased survival, blastocyst rate and live birth rate whereas the development of cryopreserved embryos from both kits seems similar. While interesting, the regulatory relevance of the study is unclear, and it is not possible to clarify which effect the HAS in the solutions have in relation to the study results. However, the study may be considered supportive of a potential clinical effect of the VitaVitro vitrification and warming solutions.

2.3.1. Discussion and conclusion on the non-clinical documentation

To conclude, the non-clinical assessment has not identified any issues which raised any concern. However, the non-clinical evidence supporting the ancillary usefulness of HSA is only inferred, as no studies have been performed which have empirically evaluated the usefulness of HSA in the solutions. Further, while the Application does include embryo-centric studies (*In vitro* mouse embryo assay and “Animal test”) there are aspects of embryonal safety which are not covered. The potential concern regarding long-term safety of removing and handling the germline, especially since many of the ART procedures occur during critical periods of epigenetic reprogramming, is acknowledged. However, these aspects are outside the scope of this consultation and, therefore, are not pursued further.

2.4. Clinical evaluation

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

Proteins are a necessary ingredient for all types of culture media and perform several important physical roles. The presence of proteins prevents embryos and gametes sticking to the devices used to collect and culture embryos. Human serum albumin (HSA) is the predominant form of protein found in human fallopian tube secretions. It is well documented that HSA can act as an antioxidant and can absorb toxins that can be detrimental to the developing embryo. HSA has a physiological function, entailing actions such as the binding of endogenous growth factors generated by embryos themselves and the chelation of heavy metals that may be present as contaminants in minute quantities in media components. Albumin binds many substances reversibly and therefore can serve as a transport or carrier protein in the body or in the culture medium. It is known that divalent cations such as zinc, cadmium, lead, and strontium inhibit pre-implantation mammalian embryo development *in vitro* and unless these cations are chelated by albumin to lower their effective concentration, they may be taken up by cells and disrupt their physiology.

There is also some evidence that embryos can directly sequester albumin and utilise the protein for metabolism. The concentrations that can be utilised by embryos are very low so that the concentrations in the media will easy supply the micronutrient.

Historically ART laboratories had the option of adding their own self-sourced albumin to ART media products, however there is no guarantee that adequate record keeping, traceability of the albumin and the quality assurance of the albumin source is maintained in these instances. It is preferable to manufacture the media products with human serum albumin incorporated and controlled by the manufacturer of these media.

EMEA Guideline PMP/PhVWP/BPWG/2231/99 rev.2 states that “to date, human albumin has not been reported to be associated with embryo-fetal toxicity”. Furthermore, when used as a protein supplement in culture media according to the appropriate procedures within an established IVF clinic, human serum albumin is not detrimental to the live birth rate.

Considering that all commercially available human IVF culture media contains human serum albumin in various forms and concentrations and that many thousands of babies were born worldwide, it can be concluded that the use of human serum albumin in IVF procedures as a protein supplement is a safe option.

The benefits of an increased success rate in embryo development with consideration to the quantity of HSA potentially transplanted into the mother at the time of embryo transplantation outweighs by the risks associated with the use of this material.

2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device

human albumin solution is frequently used as a stabiliser. The protein has amphiphilic properties, which makes it suitable as an additive to inhibit adsorption of the active protein to the container, via competitive adsorption mechanisms. The surface-active character of the protein also makes it suitable for use as a surfactant to prevent protein aggregation. HSA also has a high glass transition temperature, which in combination with its amphiphilic nature, makes it an ideal excipient for cryoprotection.

human albumin solution is one of the most widely used and characterised proteins in the pharmaceutical field. It occurs naturally in the body, as a plasma protein, with a concentration of 50 mg/mL. At this concentration, HSA regulates the colloidal osmotic pressure of blood. HSA is also responsible for transporting endogenous and exogenous compounds, which might be toxic in the unbound state, but non-toxic as albumin bound. Human serum albumin purified from plasma is used for therapeutic applications, as a plasma expander, in situations involving severe blood loss. HSA is also widely used as an excipient, especially for biotechnology products. Due to its high concentration in plasma, HSA is not associated to significant extents with safety or immunogenicity concerns.

From the Notified Body's review of the documentation in terms of potential risks to the mother and the embryo during the use of IVF Media products; bacterial contamination, viral infection and local irritant effects from the media poses the greatest risks to the health of the patient.

In conclusion, there are no new safety issues regarding use of human serum albumin identified in the VitaVitro Vitrification kit and Warming kit. The safety issue regarding parvo B19 raised in the quality assessment was adequately addressed by the applicant.

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

EMEA Guideline PMP/PhVWP/BPWG/2231/99 rev.2 states that "to date, human albumin has not been reported to be associated with embryo-fetal toxicity". Furthermore, when used as a protein supplement in culture media according to the appropriate procedures within an established IVF clinic, human serum albumin is not detrimental to the live birth rate.

Considering that all commercially available human IVF culture media contains human serum albumin in various forms and concentrations and that many thousands of babies were born worldwide, it can be concluded that the use of human serum albumin in IVF procedures as a protein supplement is a safe option.

The benefits of an increased success rate in embryo development with consideration to the quantity of HSA potentially transplanted into the mother at the time of embryo transplantation outweighs by the risks associated with the use of this material.

Notified Body Conclusion

In submitting the required information for the consultation for the VitaVitro Vitrification Kit, VitaVitro Warming Kit Media devices containing human albumin solution (HAS) the conclusion has been reached that inclusion of the ancillary human blood derivative; human serum albumin in the in-vitro fertilisation media is acceptable in terms of usefulness.

This conclusion is based on the evidence provided as part of the submission documentation for this consultation which demonstrates that the clinical benefits outweigh the risks associated with the use of the ancillary human blood derivative, human serum albumin. The Notified Body has also evaluated the potential risks associated with the safety of the medical device and is satisfied that the combination of production controls and finished product testing is appropriate to minimise any known risks to the female recipient of the ART.

2.4.4. Discussion and conclusion on the clinical evaluation

The applicant has adequately described the pharmacodynamic actions of human albumin and for its incorporation as an ancillary human blood derivate in VitaVitro Vitrification Kit and Warming Kit. The usefulness of adding human serum albumin to the media claimed by the applicant is to prevent embryos and gametes from sticking to devices, antioxidant activity and act as an embryo nutrient. The applicant has provided clinical data on usefulness/efficacy from literature, but it is not clear from the summary what the benefit of HSA would be in the device and the applicant has not provided a conclusion of the literature data. However, the established practice of serum albumin supplementation of ART media is well recognised and widely accepted. No new clinical safety issues have been identified with the use of human serum albumin in the culture media during the assessment of the current application.

Proteins are thought to stabilise the oocyte and embryonic cell membranes in an *in vitro* environment. This may be evident by improved fertilisation and embryo quality after preincubation of oocytes before ICSI or IVF. Furthermore, *in vitro* culture and recovery of frozen-thawed blastocysts for up to 20 h before transfer increased the blastocyst implantation rate three-fold. Proteins (specifically HSA) may serve as an essential and direct nutrient/nitrogen source for blastocyst stage embryos. This function may not be replaced by other macromolecular supplements.

Most embryo culture media are still supplemented with proteins rather than with nonprotein macromolecules or recombinant protein products. HSA is probably the most common supplement followed by globulin enriched preparations.

The applicant provided discussions on albumin's physiological roles, and, in addition, the medical device manufacturer submitted published literature to demonstrate the usefulness of albumin supplementation of ART media. Additionally, a clinical evaluation of the VitaVitro Vitrification kit and Warming kit was carried out in accordance with the requirements of MDR 2017/745. In summary, the conclusion of this study validated the non-inferiority of these medical devices, that is, when used for vitrification and heating human blastocysts, the vitrification medium/heating medium produced by the applicant is not inferior to similar products that are commercially available.

The medical device manufacturer outlined the well-established safety profile of human albumin and has clearly detailed the risks of human albumin used within these media, particularly the risk of transmissible infections, which is low but not non-existent. In this regard, it is recommended that the product labelling contains information outlining these risks.

Overall, the benefit-risk balance for this product is positive from a clinical point of view.

2.5. Overall conclusions

Although a full quality Module 3 for the human albumin has not been provided, all plasma used complies with the current version of the approved plasma master file (PMF). The applicant has also confirmed that human albumin product used as an ancillary substance in Vitavitro has a marketing authorisation in the EU and the information is approved and included in the MA dossier for the EU approved albumin product. Furthermore, it has also been confirmed that all albumin batches used for manufacture of VitaVitro will have an EU OCABR certificate, as required by section 6 of Annex IX to Regulation (EU) 2017/745.

The major objection raised in the Day 120 LoQ related to the missing information on nitrosamines risk evaluation has been adequately addressed. For the albumin as part of the medical device, several other

concerns were raised in the previous round, partly due to the very limited and unstructured information in some sections. These other concerns were resolved including the remaining main question at Day 180 in relation to safety margin for B19V, with the submission of an updated virus risk assessment demonstrating an adequate safety margin for B19V. The closing sequence will include this information and some minor amendments.

Overall, from a quality, non-clinical and clinical perspective, the application is recommended for positive opinion.

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 used as ancillary medicinal substance(s) in the VitaVitro Vitrification Kit, VitaVitro Warming Kit was favourable and therefore granted a positive opinion in the consultation procedure.