21 June 2023
EMA/346099/2023
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: Kitazato ART media

Ancillary medicinal substance: human albumin solution / gentamicin sulfate

Procedure No.: EMEA/H/D/006141/0000

Note

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

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Table of contents

1. Background information on the procedure....4
1.1. Submission of the dossier....4
1.2. Steps taken for the assessment of the product....4
1.3. Manufacturers....5
1.4. Remarks to the notified body....6
1.5. Recommended measures to the notified body....7
2. Scientific overview and discussion....7
2.1. General information....7
2.2. Quality documentation....10
2.2.1. For the ancillary medicinal substance or the ancillary human blood derivative itself....10
2.2.2. For the ancillary medicinal substance or the ancillary human blood derivative as incorporated in the medical device....10
2.2.3. Discussion and conclusion on <chemical, pharmaceutical and biological aspects>....11
2.3. Non-clinical documentation....11
2.3.1. Discussion and conclusion on the non-clinical documentation....14
2.4. Clinical evaluation....15
2.4.1. Usefulness of the ancillary medicinal substance incorporated in the medical device as verified by notified body....15
2.4.2. Clinical safety of the ancillary medicinal substance incorporated in the medical device....16
2.4.3. Clinical benefit/risk profile of the ancillary medicinal substance incorporated in the medical device....16
2.4.4. Discussion and conclusion on the clinical evaluation....16
2.5. Overall conclusions....17
2.6. Recommendation....17

1. Background information on the procedure

1.1. Submission of the dossier

The notified body KITAZATO Corporation submitted to the European Medicines Agency (EMA) on 25 May 2022 an application for consultation on human albumin solution / gentamicin sulfate incorporated as ancillary medicinal substance(s) in the medical device Kitazato ART media, 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 and the evaluation teams were:

Rapporteur: Kristina Dunder Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	25 May 2022
The procedure started on	14 July 2022
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 October 2022
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	14 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 February 2023
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	03 April 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 April 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 May 2023
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 June 2023
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 / gentamicin sulfate as ancillary medicinal substance(s) used in Kitazato ART media on	21 June 2023

1.3. Manufacturers

Manufacturers of the active substance used as ancillary medicinal substance

Fujian Fukang Pharmaceutical Co. Ltd
Jiangyin Industrial Estate
Fuqing
350309 Fuzhou
CHINA

Grifols Therapeutics, Inc.
US 70 Bus Hwy 8368
Clayton, NC-27520
UNITED STATES

Instituto Grifols, S.A.
Poligono Ind. Levante
c/Can Guasc 2
Parets del Valles
08150 Barcelona
SPAIN

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
SWEDEN

Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaer Strasse 235
1100 Vienna
AUSTRIA

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

Grifols Therapeutics, Inc.
US 70 Bus Hwy 8368
Clayton, NC-27520
UNITED STATES

Instituto Grifols, S.A.
Poligono Ind. Levante
c/Can Guasc 2
Parets del Valles
08150 Barcelona
SPAIN

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
SWEDEN

Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaer Strasse 235
1100 Vienna
AUSTRIA

Manufacturers responsible for batch release

Instituto Grifols, S.A.
Poligono Ind. Levante
c/Can Guasc 2
Parets del Valles
08150 Barcelona
SPAIN

Octapharma Pharmazeutika Produktionsges.m.b.H
Oberlaaer Strasse 235
1100 Vienna
AUSTRIA

Octapharma AB
Lars Forssells gata 23
112 75 Stockholm
SWEDEN

Octapharma Dessau GmbH
Otto-Reuter-Strasse 3,
Dessau-Rosslau, Sachsen-Anhalt,
06847 Germany

Pharma Generics B.V
Amsterdamseweg 204a
Amstelveen, 1182 HL,
The Netherlands

Manufacturer(s) of the medical device

Kitazato Corporation
100-10 Yanaguishima
Fuji
Shizuoka 416-0932
Japan

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.

1.4. Remarks to the notified body

1. Details of measures to control sterility (e.g. aseptic processing, sterile filtration of components added, final sterile filtration and validation thereof) are very limited and should be addressed.

2. For Quality Control (QC) testing of Kitazato ART media containing human serum albumin, a cytotoxicity Mouse Embryo Assay (MEA) and a human sperm survival assay (HSSA) are performed. Validation data was not provided for these assays. The Notified body is advised that for medicinal products, QC testing methods should be validated, and the relevant results have to be provided in the dossier. Particular attention is paid to validation of non-compendial biological methods.

3. It is not clear where QC testing of the devices takes place; this point should be clarified and assurance provided that the relevant standards are in place at the site(s). If relevant and applicable to medical devices, the results of method transfer for non-compendial methods should be presented.

1.5. 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[1]	Description
Quality	It is emphasised that the overall risk of nitrosamine impurities is not linked only to ancillary substances and their incorporation and that changes to device processes in the future may modify the risk. It is assumed that the Notified Body has complete oversight on the entirety of the risks (including factors aside from the ancillary substances) and follows up on the evolution of risks during surveillance inspections.
Quality	The notified body should follow up that testing of gentamicin in accordance with the Ph. Eur. and the CEP is performed by third party accredited laboratory on behalf of the manufacturer KITAZATO and that the outcome of the tests is acceptable.
Labelling	Although the performed Sensitization test (guinea pig maximisation test, GPMT) study on the final device gave negative results, the Information for users (IFU) should include a warning to inform the mother-to-be of the presence of gentamicin in relation to the potential hypersensitivity reactions, as a mitigation risk measure.

[1] Areas: quality, safety, including clinical benefit/risk profile.

2. Scientific overview and discussion

2.1. General information

The notified body BSI Group submitted to the European Medicines Agency (EMA) on 25 May 2022 an application for consultation on human serum albumin (HSA) and gentamicin, as ancillary medicinal substance(s) used in the medical device portfolio KITAZATO HSA-containing Artificial Reproductive Techniques (ART) Media, in accordance with the procedure falling within the scope of Regulation (EU) 2017/745.

Kitazato ART media supplemented with HSA and/or gentamicin are a range of media products designed for use in Assisted Reproduction Technologies (ART) (Table 1). They have direct physical contact with human gametes or embryos for the purposes of preparation, maintenance, transfer, or storage. During intrauterine insemination or embryo transfer, the media might come in contact with the uterus mucosal membrane.

Human serum albumin is a constituent of normal blood which is a well-known substance used in In Vitro Fertilisation (IVF) media for over 20 years. Historically, media have been supplemented with protein in the form of either serum albumin or serum. Albumin is universally added to most ART media because it is widely considered to be of benefit and the use of human albumin solution in embryo culture media has been recommended by the European Society of Human Reproduction and Embryology (ESHRE). The principal roles of ART media products are to support the development of gametes and embryos during the procedures used for assisted reproduction. The beneficial ancillary action of human albumin in KITAZATO HSA-containing ART media includes:

- pH regulator

- Osmotic regulator
- Stabilization of cell membrane
- Nutrient and carrier of growth promoting substances (i.e. amino acids, vitamins, fatty acids, hormones, growth factors)
- Aid in fertilization process (important in the process of sperm capacitation and/or the acrosome reaction)
- Scavenger (of for example toxins and waste products from cell metabolism)
- Surfactant (anti-adhesion), thereby facilitating gamete and embryo manipulation
- Cryoprotectant (increase viscosity of cryoprotectant solution, only applicable in Sperm Freezing media)

The intended action of adding gentamicin sulfate to Kitazato ART media is not to treat a disease, but to avoid the bacterial infection of (sterile) cell cultures during normal handling under strict hygienic conditions. Kitazato ART media supplemented with HSA and/or gentamicin are not administered to patients, but as these products can be used during in-vitro fertilization procedures ending in embryo transfer and/or intrauterine insemination (IUI), so very small amounts might be transferred into the women reproductive tract.

Table 1. Overview of Kitazato ART media

Kitazato ART media	Intended use
Gamete Buffer Media: - Gamete Buffer medium - SepaSperm Wash medium	Gamete Buffer media are ready-to-use cell culture media with the following purposes: - Washing of human ova - Washing of spermatozoa - Washing of human embryos - Swim-up of spermatozoa - Embryo transfer - Fertilization by intracytoplasmic sperm injection (ICSI) - Intra-uterine insemination (IUI) - Production of density gradients, e.g., with SepaSperm Media
Fertilization Media	Fertilization media are bicarbonate buffered cell culture media for washing and holding human oocytes, performing fertilization by IVF or ICSI (until 2PN stage).
Single Step medium	Single Step medium is a ready-to-use bicarbonate-buffered single-step culture medium, designed for the handling of oocytes (in preparation of, or during IVF/ICSI or IUI), for fertilization, and for embryo culture from day 1 to expanded blastocyst stage. It can also be used for embryo transfer. Single Step medium may also be used for the processing of semen. It can be used in combination with a density gradient and/or swim-up procedure.
Sperm Freeze media	SpermFreeze media are cell culture media for the cryopreservation of human spermatozoa. SpermFreeze can also be used for cryopreservation of tissue and sperm from testicular biopsies.
PVP	PVP medium is a ready-to-use viscous medium that can be used in ICSI procedures. These procedures require the capture of individual sperm cells in a pipette for injection into the oocyte. This is facilitated by first immobilizing the sperm by placing them in a viscous medium prior to nicking the tail to immobilize the sperm completely.
Hyaluronidase	Hyaluronidase medium is typically used in the oocyte denudation process for the digestion of the hyaluronic acid between cumulus cells.
SepaSperm Media: - SepaSperm Solution - SepaSperm 45% - SepaSperm 90%	SepaSperm Media are discontinuous gradient systems which effectively separate spermatozoa from seminal plasma. During centrifugation, cells move through the discontinuous density gradient to the point in the gradient which matches their own density. SepaSperm Media can be used in as sperm preparation method for further use in Intra Uterine Insemination (IUI), In Vitro Fertilization (IVF) Intra-Cytoplasmic Sperm Injection (ICSI), and related Assisted Reproductive Technologies (ART).

2.2. Quality documentation

2.2.1. Introduction (quality aspects)

This is an application for consultation on human serum albumin (HSA) and gentamicin, as ancillary medicinal substances used in the medical device portfolio KITAZATO HSA-containing Assisted Reproductive Techniques (ART) Media. As albumin is sourced from two providers, the provided information is assessed separately resulting in three sections on ancillary medicinal substance (i.e. gentamicin, human albumin solution Albunorm 25% (250 g/l) Octapharma and human albumin solution Plasbumin 25% Grifols).

2.2.2. For the ancillary medicinal substance - gentamicin sulfate

2.2.2.1. Introduction

Kitazato ART media supplemented with antibiotics are a range of media products designed for use in Assisted Reproduction Technologies (ART). They have direct physical contact with human gametes or embryos for the purposes of preparation, maintenance or transfer or storage. The media consist of various compositions of physiological salts, nutritional and energy substances and buffer systems. Since these media contain gentamicin sulfate (as ancillary medicinal substance), they are considered Class III medical devices according to Rule 14 of the European Medical Device Regulation 2017/745. All media are used in specialized hospital laboratories by laboratory technicians applying ART.

2.2.2.2. Active substance

Gentamicin sulfate is supplied by Fujian Fukang Pharmaceuticals Co. Ltd. using a Certificate of Suitability (CEP) procedure; R1-CEP 1998-155-Rev 10. The gentamicin sulfate is controlled by the supplier in line with the Ph. Eur. and additional tests for histamine as per the CEP. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

A nitrosamines risk evaluation performed in accordance with Questions and answers on “Information on nitrosamines for marketing authorisation holders” (EMA/409815/2020) and Nitrosamine Impurities - Final Outcome of Article 5(3) (EMA/369136/2020) has been provided and found acceptable. The risk of presence of nitrosamine impurities is negligible and routine testing for nitrosamine impurities is not required.

Gentamicin sulfate is of acceptable quality. Regarding the quality control testing of gentamicin sulfate, device manufacturer will perform quality control through third party accredited laboratory to provide additional assurance that gentamicin complies with Ph. Eur. monograph. This point was captured as a recommended measure to the notified body. Considering the type of medical device and intended use, this approach was considered acceptable.

Acceptable stability data according to ICH requirements have been provided. All results are well within the specification limits in the Ph. Eur. monograph and no trends are seen. The proposed shelf-life of 4 years with no temperature restrictions is supported.

Gentamicin sulfate is derived from fermentation of the bacteria *Micromonospora purpurea* and one of the nutrients included in the fermentation medium is fish peptone. A viral safety risk assessment is provided by the supplier of gentamicin sulfate addressing both the manufacturing process of the fish peptone and the extraction process for the gentamicin sulfate. The risk assessment supports the

conclusion of very low risk of viral contamination. A transmissible spongiform encephalopathies (TSE) statement from the supplier of gentamicin sulfate is also provided. The information is sufficient.

The gentamicin sulfate active substance is incorporated into the medical device media. Therefore module 3.2.P for gentamicin sulfate is not applicable.

2.2.3. For the ancillary human blood derivative itself – human albumin solution Albunorm 25% (250 g/l) Octapharma

2.2.3.1. Introduction

The human albumin 25% from Octapharma used in the medical device is stated to be Albunorm 250 g/l.

2.2.3.2. Active substance

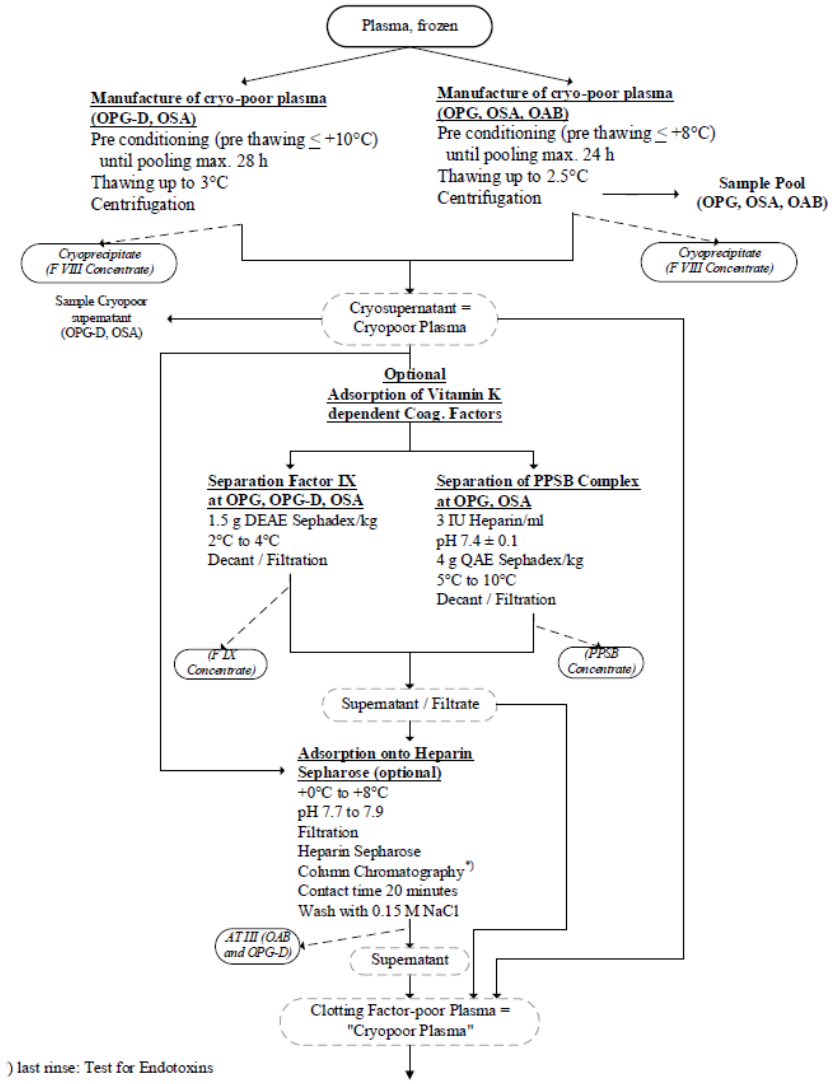
Manufacture

The following manufacturers have been listed as active substance manufacturers

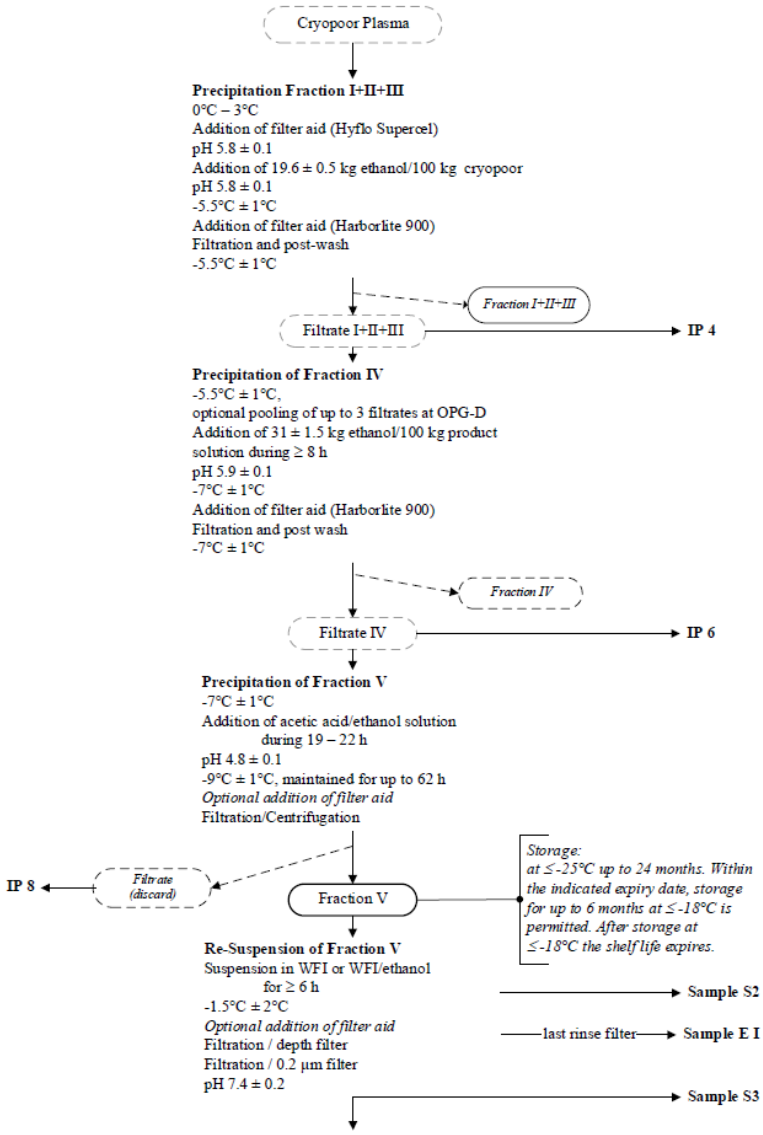
Site	Responsibilities
Octapharma – Vienna (OPG) Octapharma Pharmazeutika Produktionsges.m.b.H Oberlaaer Straße 235 1100 Vienna Austria	Production from plasma to final product, visual inspection, labelling and packaging for products from all sites, batch release.
Octapharma – Stockholm (OAB) Octapharma AB 112 75 Stockholm Sweden	Production from plasma to final product, visual inspection, labelling, packaging, batch release.

The GMP compliance of the manufacturing sites has been assessed and no GMP compliance issues for these sites were identified.

A flowchart and a detailed descriptions of the manufacturing steps is provided below.



*) last rinse: Test for Endotoxins


Cryopoor Plasma
Precipitation Fraction I+II+III
0°C – 3°C
Addition of filter aid (Hyflo Supercel)
pH 5.8 ± 0.1
Addition of 19.6 ± 0.5 kg ethanol/100 kg cryopoor
pH 5.8 ± 0.1
-5.5°C ± 1°C
Addition of filter aid (Harborlite 900)
Filtration and post-wash
-5.5°C ± 1°C
Fraction I+II+III
Filtrate I+II+III
IP 4
Precipitation of Fraction IV
-5.5°C ± 1°C,
optional pooling of up to 3 filtrates at OPG-D
Addition of 31 ± 1.5 kg ethanol/100 kg product
solution during ≥ 8 h
pH 5.9 ± 0.1
-7°C ± 1°C
Addition of filter aid (Harborlite 900)
Filtration and post wash
-7°C ± 1°C
Fraction IV
Filtrate IV
IP 6
Precipitation of Fraction V
-7°C ± 1°C
Addition of acetic acid/ethanol solution
during 19 – 22 h
pH 4.8 ± 0.1
-9°C ± 1°C, maintained for up to 62 h
Optional addition of filter aid
Filtration/Centrifugation
IP 8
Filtrate
(discard)
Fraction V
Storage:
at ≤-25°C up to 24 months. Within the indicated expiry date, storage for up to 6 months at ≤-18°C is permitted. After storage at ≤-18°C the shelf life expires.
Re-Suspension of Fraction V
Suspension in WFI or WFI/ethanol
for ≥ 6 h
-1.5°C ± 2°C
Optional addition of filter aid
Filtration / depth filter
Filtration / 0.2 µm filter
pH 7.4 ± 0.2
Sample S2
last rinse filter
Sample E I
Sample S3

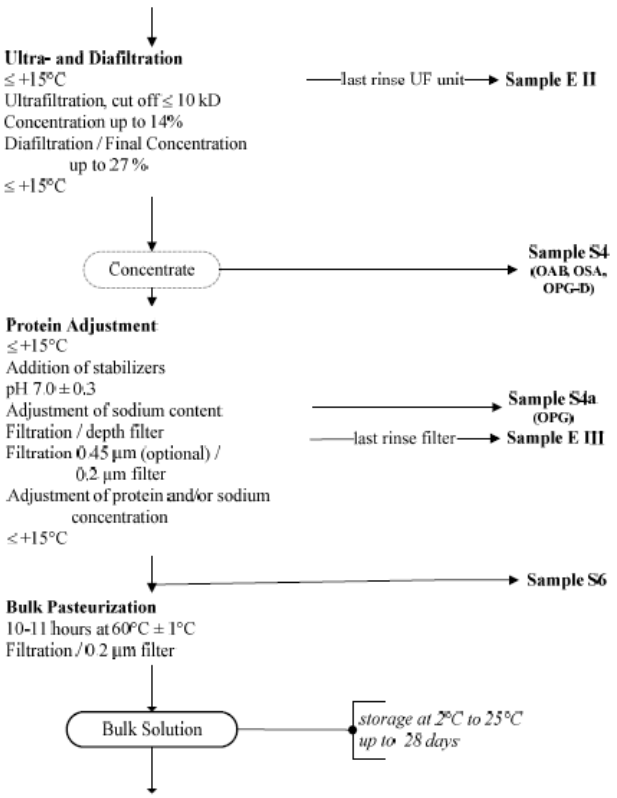


Figure 1: Manufacturing process of human albumin solution Albunorm 25 % (250 g/l) Octapharma

The active substance human albumin is isolated and purified by the cold ethanol fractionation process from a pool of human plasma. In this process, after separation of the cryoprecipitate by centrifugation the ethanol concentration is raised stepwise from 0 to 40 vol %, the temperature is lowered from +1 to -9°C, and the pH is lowered from between 7.0 and 8.0 to 4.8. The protein fractions precipitate during this process, and after each precipitation stage they are separated from the protein solution either by centrifugation or filtration. After suspension of the fraction V the solution is ultrafiltered to remove the ethanol and precipitation salts and to reduce the volume of the solution. A subsequent diafiltration removes the residues of ethanol and reduces the aluminium content to < 200 g/l.

The manufacturing process is controlled by in-process testing in all critical steps throughout the process. A list of in-process controls at respective step and limits has been provided and found acceptable. Sufficient description of the process and controls has been provided.

Detailed information on process validation has been provided for all manufacturing sites. Separate validation reports have been provided for subsequent changes in the process such as increased batch size, use of a heparin sepharose column as an adsorption step, change in filtration steps (new filters) etc.. Sufficient data from process validations has been provided to support consistency in manufacture of Albunorm.

Starting material

All plasma used for the manufacture of Albunorm complies with the current version of the approved Plasma Master File (PMF). The PMF certificate no: EMEA/H/PMF/000008/05/AU/28/G, issued 27 Jan 2022 has been provided.

Specifications

Specifications for albumin 25% bulk is presented in the table below.

Table 2. Specifications for albumin 25 % bulk

Tests		
Total protein:	Ph.Eur. (Biuret) (2.5.33)	23.8 – 26.2 % (w/v)
Molecular size distribution: (Polymers and aggregates)	Ph. Eur. (2.2.29)	≤ 10% of the total chromatogram area (corresponds to about 5% of polymers and aggregates)
Sodium:	Ph.Eur. (2.2.22)	144 – 160 mmol/l
Potassium:	Ph.Eur. (2.2.22)	≤ 12.5 mmol/l
pH value:	Ph.Eur. (2.2.3)	6.7 – 7.3
Osmolality:	Ph.Eur. (2.2.35)	250 – 400 mosmol/kg
Density:	Ph. Eur. (2.2.5)	> 1.0500 g/ml
Caprylic acid:	Ph. Eur. (2.2.28)	0.064 – 0.096 mmol/g protein
N-Acetyl-DL-tryptophan:	Ph. Eur. (2.2.29)	0.064 – 0.096 mmol/g protein
TVC:	Ph. Eur. (2.6.12)	≤ 10 CFU/100ml

The bulk specification for Albunorm 25 % fulfils the requirements in the European Pharmacopoeia (Ph. Eur.). The stated limits are both release- and shelf-life limits.

Method descriptions and validation reports for all test methods have been provided except for molecular size distribution, caprylic acid and N-acetyl-DL-tryptophan. However, the same tests are performed on finished product and descriptions and validation reports for these methods are provided in finished product sections and are discussed there. This is acceptable.

Sufficient information is provided on reference standards.

Container Closure System

During the manufacture, the albumin bulk may be stored in insulated stainless steel tanks prior to filling or the filtered solution is filled into appropriate transport containers and transferred to the respective plants for filling.

In the stability studies included in S.7, container used are listed as disposable plastic container, Flexboy and single use bags made of a low-density polyethylene (LDPE) film. Provided information was considered acceptable.

Stability

Stability data has been provided for Albunorm 25% (250g/l) bulk solution stored in in the disposable plastic container. Flexboy and single use bags made of a low-density polyethylene (LDPE) film. For these containers, sufficient data has been provided to support the shelf life of 28 days at 2° C – 25 °C.

2.2.3.3. Finished product

Composition

Albunorm 25% is a solution for infusion. The route of administration is intravenous. The composition of Albunorm 25% is presented in the table below.

Name of Active Ingredients	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Plasma proteins with at least 96% human albumin	250 g	Active Ingredients	Internal
Name of Excipients	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Sodium[1]	144-160 mmol	osmotic and electrolyt component	Ph. Eur
N-acetyl-DL-tryptophan	16-24 mmol	Stabiliser	Ph. Eur.
Caprylic acid	16-24 mmol	Stabiliser	Ph. Eur.
Water for injections	ad 1000 ml	Solvent	Ph. Eur.
Name of other Components	**Quantity per 1000 ml**	**Function**	**Reference to Standards**
Potassium[2]	≤ 12.5 mmol	osmotic and electrolyt component	Ph. Eur

[1]Sodium is added to the solution as sodium chloride and also as part of different buffer solutions. The quantity of sodium chloride varies depending on the sodium content on the solution in order to adjust to the requested final concentration of 144-160 mmol sodium per l protein solution.

[2]Potassium is a component of the human plasma starting material and not actively added as excipient.

Pharmaceutical development

The active substance human albumin bulk is isolated and purified by the cold ethanol fractionation process from a pool of human plasma. Albunorm 25% w/v (250g/l) contains the following excipients: N-acetyl-DL-tryptophan, caprylic acid, sodium, and water for injections. All excipients are of pharmacopoeia quality.

The excipients N-acetyl-DL-tryptophan, caprylic acid and sodium and the corresponding limits are described in the Ph. Eur. and the USP. The concentrations of the stabilisers have proven to be suitable for the stabilisation of albumin during pasteurisation.

The shelf life is based on the results of stability study provided in sections 3.2.P.8. of the dossier. The results show no significant change of the product quality and support a proposed shelf life.

Manufacturers

The manufacturers and testing facilities of Albunorm 25% w/v (250g/l) are listed in the table below.

Table 3. Manufacturers and testing facilities of Albunorm

Site	responsibilities
Manufacturer: Octapharma – Vienna Octapharma Pharmazeutika Produktionsges.m.b.H	Production from plasma to final product, visual inspection for products from all sites, labelling

Oberlaaer Straße 235 1100 Vienna Austria	and packaging for products from all sites, batch release
Manufacturer: Octapharma – Stockholm Octapharma AB 112 75 Stockholm Sweden	Production from plasma to final product, visual inspection, labelling, packaging, batch release
Octapharma – Dessau Octapharma Dessau GmbH Otto-Reuter-Str. 3 06847 Dessau Germany	Visual inspection for products from all sites, Packaging, Labelling
Octapharma AG Octapharma AG Siedenstrasse 2 8853 Lachen Switzerland	Secondary packaging

The GMP compliance of the manufacturing sites has been assessed and no GMP compliance issues for these sites were identified.

Manufacture

Flow chart and detailed description of respective step has been provided in Figure 2.

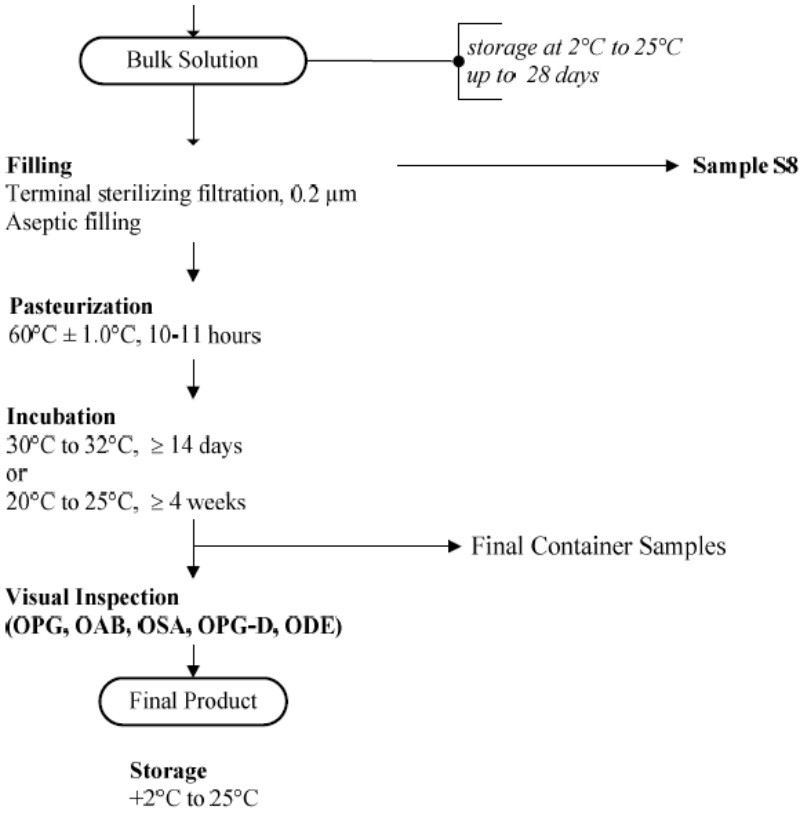


Figure 2: Manufacturing process flow chart of Albunorm 250 g/l finished product

The process consists of sterile filtration of the bulk, aseptic filling containers followed by pasteurisation and subsequent incubation and visual inspection.

In-process control results and in process test methods and validations have been provided. Process validation data has also been provided for the steps included in the finished product process. Acceptable information has been provided for the manufacturing process.

Specifications

The specification for Albunorm 25% w/v (250 g/l) is presented below.

Table 4. Specification for Albunorm 250 g/l

Characters		
	Ph. Eur.	**A clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.**
Identification		
Immunoelectrophoresis:	Ph. Eur.	**Strong albumin precipitation band with anti-human-serum.**
Tests		
pH value:	Ph. Eur. (2.2.3)	**6.7 – 7.3**
Total protein:	Ph. Eur. (Biuret) (2.5.33)	**23.8 – 26.2 % (w/v)**
Protein composition:	Electrophoresis	**≥ 96 % albumin**
Molecular size distribution: (Polymers and aggregates)	Ph. Eur. (2.2.30)	**≤ 10% of the total chromatogram area (corresponds to about 5% of polymers and aggregates)**
Haem content:	Ph. Eur. (2.2.25)	**Absorption: ≤ 0.150**
Prekallikrein activator:	Ph. Eur. (2.6.15)	**≤ 35 IU/ml**
Aluminium:	Ph. Eur. (2.2.23)	**≤ 200 µg/l (ppb)**
Potassium:	Ph. Eur. (2.2.22)	**≤ 12.5 mmol/l**
Sodium:	Ph. Eur. (2.2.22)	**144 – 160 mmol/l**
Sterility:	Ph. Eur. (2.6.1)	**Sterile**
Endotoxin:	Ph. Eur. (2.6.14)	**< 1.7 IU/ml**
Additional Tests		
N-Acetyl-DL-tryptophan:	Ph. Eur. (2.2.29)	**0.064 – 0.096 mmol/g protein**
Caprylic acid:	Ph. Eur. (2.2.28)	**0.064 – 0.096 mmol/g protein**
Osmolality:	Ph. Eur. (2.2.35)	**250 – 400 mosmol/kg**

The finished product specifications (FPS) for Albunorm 25 % fulfil the requirements in the European Pharmacopoeia (Ph. Eur.) Monograph 01/2013:0255. The stated limits are both release- and shelf-life limits.

Acceptable method description and validation reports have been provided for all test methods. Acceptable batch data has also been provided.

Several reports for characterisation of impurities have been provided, including impurities for optional steps including studies of leachables from chromatography columns used.

A risk evaluation regarding nitrosamines for the Albunorm product has then been provided. This evaluation was performed in line with EMA/409815/2020, Octapharma considered the manufacturing process itself, process condition, contamination risks from process water, excipients and primary packaging material in the evaluation to identify any risks for nitrosamines in the finished product. The provided information is acceptable.

Container Closure System

Tables listing all infusion bottles and respective suppliers has been provided. All infusion bottles are of type II glass and complying with Ph. Eur. Detailed information is also provided for the stoppers used (Type I). Also, the stoppers comply with Ph. Eur. Requirements.

The bottles are sealed with aluminium flip-off caps.

Information on container closure system is found acceptable.

Stability

The shelf-life of Albunorm is 36 months at +2°C to +25°C, protected from light.

Several stability studies performed in compliance with current requirements, both long term studies and accelerated studies. The stability data on which the summary and conclusion is based, is included in the dossier. Taking into account also the other supportive stability studies on Albunorm 5% and Albunorm 20% as well as the former long-lasting experience with albumin 25% final product the following shelf life can be supported. Sufficient stability data has been provided to support the shelf-life.

2.2.3.4. Adventitious agents' safety

The pathogen safety statement provided by Octapharma includes a summary of the virus validation studies and strategy.

The testing of donations and plasma pools are covered by the EU approved Octapharma PMF.

The overall pathogen safety of Albumin is based on two distinct process steps with different modes of action:

Step 1: Cold ethanol fractionation

Step 2: Final container pasteurization

To reduce the risk of viral cross-contamination during filling, an additional in-process bulk pasteurization step is applied.

Table 5. *Pathogen Clearance Results (EU approved)*

Pathogen human	HIV-1/2	HBV	HCV, WNV	HAV	B19V	Prion
(Relevant model)	(HIV-1)	(PRV)	(SBV)	(MEV)	(PPV)	(HAS 263K)
Manufacturing step	Logarithmic reduction factor (LRF) [log_{10}]					
Cold ethanol precipitation	4.98	≥ 5.70	5.89	2.88	3.52	≥ 3.86
Final container pasteurization	≥ 7.23	≥ 8.67	≥ 8.79	3.70	2.25	n/a
Global reduction factor	**≥ 12.21**	**≥ 14.37**	**≥ 14.68**	**6.58**	**5.77**	**≥ 3.86**

HIV-1: Human immunodeficiency virus type 1, model for HIV type 1 and HIV type 2
PRV: Pseudorabies virus, model for e.g., hepatitis B virus (HBV)
SBV: Sindbis virus, model for e.g., hepatitis C virus (HCV) and West Nile virus (WNV)
MEV: Mouse encephalomyelitis virus, model for hepatitis A virus (HAV)
PPV: Porcine parvovirus, model for human parvovirus B19 (B19V)
HAS 263K: hamster-adapted scrapie strain 263K, model for prions
n/a: not applicable
≥: pathogen reduction below the detection limit

Acceptable information has been provided for the virus validation studies.

A description of the estimation of risk of transmission of vCJD by Albunorm has also been provided demonstrating that the risk is negligible.

2.2.4. For the ancillary human blood derivative itself – human albumin solution Plasbumin 25% Grifols

2.2.4.1. Introduction

A module 2 Quality overall summary has been provided for Plasbumin 25% Grifols. In addition, an abridged / mini module 3 has been provided. In the module 2 (M2) provided (also referred to as Albumin 25% low aluminium), only one manufacturing process is described (acetone process). However, in the more detailed sections provided in the mini-module 3, a different acetone-free manufacturing process is described which differs from the process described in M2. The finished product specifications for the acetone-free process also differs from the specifications presented in M2.

The uncertainty regarding the manufacturing process for the Plasbumin 25% Grifols gave rise to a major objection requesting confirmation that this process is included in the approved EU dossier for the Plasbumin product. In the response, it was clarified that Only the acetone-free process is used for manufacture of Plasbumin 25% used for Kitazato (and that the acetone-free process is approved in the EU for the Plasbumin Grifols product). The information from Grifols has then been updated resolving the major objection. The module 3 contains the following sections:

- manufacturing process and flow
- shelf-life specifications
- stability data

- viral safety
- description and composition

This approach was found acceptable.

2.2.4.2. Active substance

Manufacture

The active substance is defined as the final sterile bulk before filling into the final container.

The manufacture and/or analytical testing of the active substance are performed at:

Grifols Therapeutics (GT)
8368 US 70 Business Hwy.West
Clayton, North Carolina 27520
United States

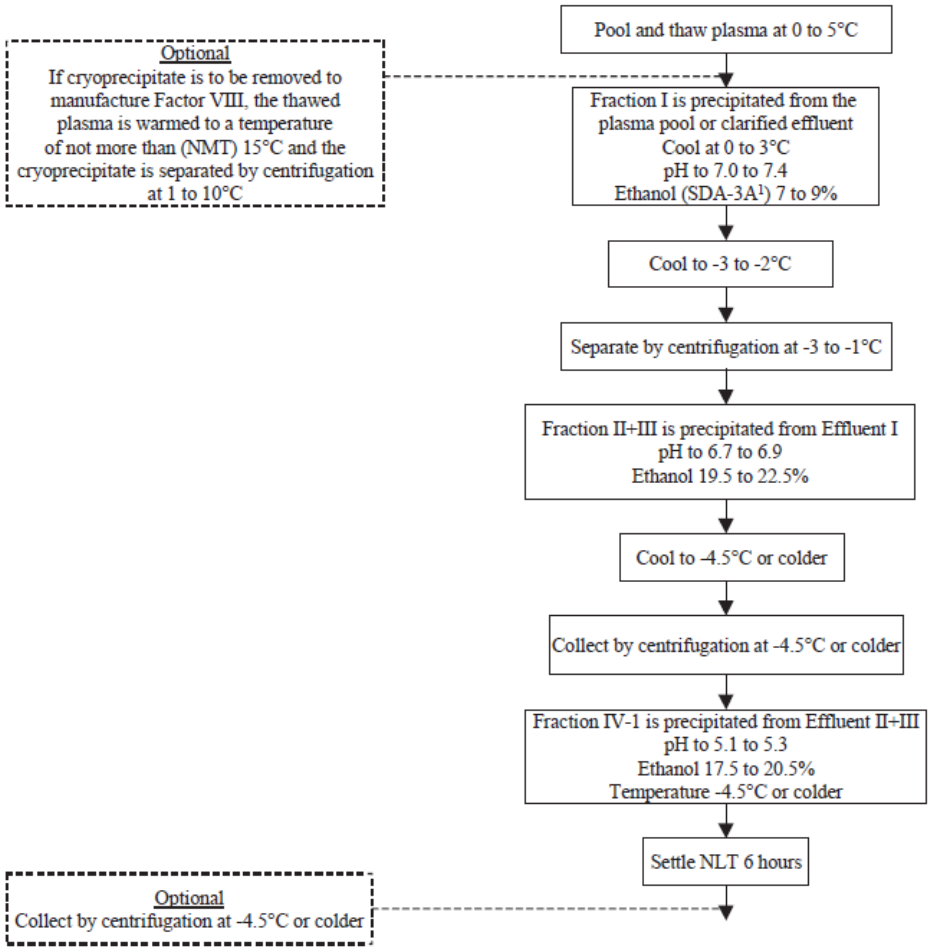
Instituto Grifols, S.A.
Poligono Ind. Levante
c/Can Guasc 2
Parets del Valles
08150 Barcelona
SPAIN

The manufacture of the sterile bulk is basically performed by modified Cohn-Oncley fractionation followed by further purification steps. The fractionation starts with pooling of plasma and ends with collection of fraction V paste which can be stored at -20°C for up to 36 months at -20°C.

For further purification of the albumin, the dissolved fraction V is clarified by depth filtration and concentrated by diafiltration. The final bulk is prepared by adding sodium caprylate, N-acetyl-DL-tryptophan, sodium hydroxide, sodium chloride. The bulk is then heat treated at 59-61°C for 4 hours.

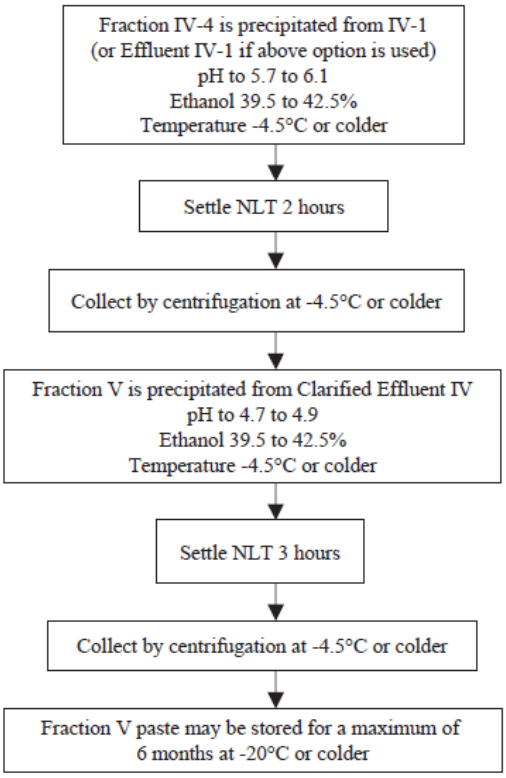
The solution is sterile filtered and may be stored 30 days at 2-8°C prior to filling into final containers. After further dept filtration and adjustment of stabilisers, pH and protein concentration, the bulk is sterile filtered. The sterile bulk can be held up to 7 days 2-8°C.

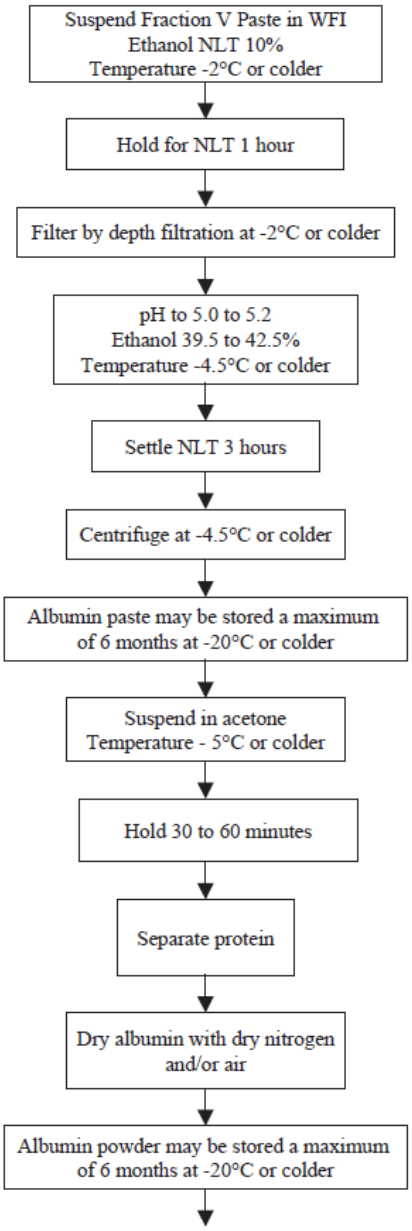
Manufacturing process flow chart is provided in figure 3.



[1]Specially Denatured Alcohol - (95% ethanol, 5% methanol)

Fractionation Flow Diagram
Continued




Suspend Fraction V Paste in WFI
Ethanol NLT 10%
Temperature -2°C or colder
Hold for NLT 1 hour
Filter by depth filtration at -2°C or colder
pH to 5.0 to 5.2
Ethanol 39.5 to 42.5%
Temperature -4.5°C or colder
Settle NLT 3 hours
Centrifuge at -4.5°C or colder
Albumin paste may be stored a maximum of 6 months at -20°C or colder
Suspend in acetone
Temperature - 5°C or colder
Hold 30 to 60 minutes
Separate protein
Dry albumin with dry nitrogen and/or air
Albumin powder may be stored a maximum of 6 months at -20°C or colder

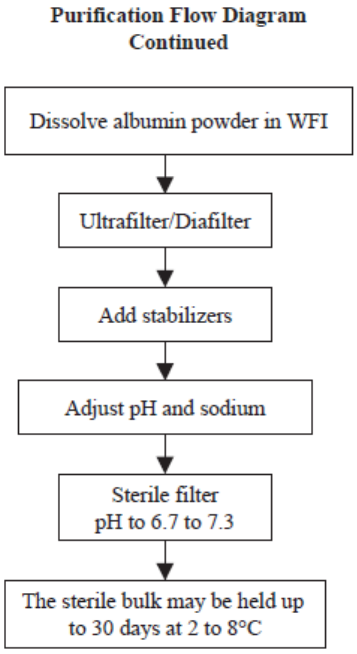


Figure 3: Manufacturing process flow chart

Sufficient details have been provided for the description of the manufacturing process. The manufacturing formula is also presented.

All raw materials are presented in tables with quality standard given.

Starting material

Human plasma complies with Ph. Eur. All other starting materials except denatured alcohol meet the requirements of Ph. Eur. or other monographs. Specifications have been set for denatured alcohol and acceptable specifications have been provided.

Instituto Grifols, S.A. has also provided a Letter of Access for their Plasma Master File EMEA/H/PMF/000002/04/II/034/G and confirm that the PMF certificate, evaluation report and PMF dossier are fully applicable for the ancillary human blood derivative.

Process validation

To ensure consistent and reproducible processing of the product manufacturing steps are monitored by in-process controls. Microbiological quality is monitored throughout these processes to ensure the necessary controls are in place to minimize the potential for product contamination.

Validation of the manufacturing process beginning with the starting plasma pool through the sterile filtration of the formulated bulk. A series of not less than (NLT) three consecutive qualification runs were performed for each system of the Albumin product stream. Approved batch production records (BPRs) were used throughout the process performance qualification (PPQ). 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. The results of PPQ testing demonstrated that the process produces intermediates and final product that meet predetermined specifications and quality attributes.

Specifications

The active substance (the final sterile bulk) is tested for protein composition by capillary zone electrophoresis (CZE). With CZE, the movement of charged particles within a narrow bore tube is used to analyse the protein composition. The specification for the bulk has been set at not less than 96% albumin.

The protein composition method, CZE, has been validated for Albumin (Human) products.

Considering the continuous nature of the manufacturing process and that quality attributes were tested on the finished product level, this approach was found acceptable.

Container closure system

Various size stainless steel bulk tanks are used to store final bulk product in a nominal 5°C Class C area. Each tank is maintained under positive air pressure and is vented by a 0.2 µm filter. Each tank is sterilized prior to use. Provided information is acceptable.

Stability

Studies were performed to verify the sterility of the product stored in various sized stainless steel bulk tanks. Empty sterile bulk tanks were stored in a 2 to 8°C room for not more than (NMT) seven days after sterilization and then filled with sterile filtered growth media. The bulk tanks were subsequently stored at ambient temperature for a period of five days. After the initial five day ambient storage period, the bulk tanks were transferred to a 2 to 8°C storage room for a period of at least ninety days.

Based on the results, sterile bulk tanks used to store Albumin (Human) sterile bulk product demonstrated that the bulk tanks can be used to store sterile media for NMT 5 days at ambient temperature and NMT 90 days at a controlled temperature of 2 to 8°C with no adverse effect on the sterility of the media.

Evaluations were performed to establish both the shelf-life and storage conditions for the active substance. Batches for active substance stability studies were manufactured at the production facility in Clayton, North Carolina, USA with a scaled-down model of the container/closure system used with the marketed product.

All data for the active substance met the established acceptance criteria for pH and aggregates throughout the duration of the studies. No significant changes in molecular weight distribution for the sterile active substance samples were observed through 30 days of storage at 5°C.

2.2.4.3. Finished product

Composition

Albumin (Human) 25% (also named Plasbumin 25% Grifols or Human Albumin Solution L/A 25% throughout this section) is a clear, slightly viscous, pale yellow to amber or green liquid.

The composition of the finished product is presented below.

Table 6. Composition of Albumin (Human) 25% (Plasbumin 25% Grifols) finished product

Size	Active Ingredients	Other Ingredients			
	Albumin[a]	Sodium Caprylate	N-Acetyl-DL-Tryptophan	Sodium[b]	Water for Injection (WFI)
mL	0.25 g	0.00332 g	0.00493 g	0.00333 g	q.s. to 1 mL
Function	Active ingredient	Stabilizer	Stabilizer	Tonicity	Solvent
Reference to Standard	EP	NF/EP	EP	----[c]	USP/EP

[a] Not less than 95% of the protein has the electrophoretic mobility of albumin.

[b] Value represents sodium ion concentration from all sources.

[c] Complies with specifications.

Detailed information on the type of container closure has also been provided.

Manufacturers

Manufacturers involved in manufacture are outlined below

Table 7. Manufacturers for Human Albumin Solution L/A 25% (Plasbumin 25% Grifols)

Name	Address	Responsibility
Talecris Biotherapeutics, Inc.	8368 US 70 West Clayton, North Carolina, USA 27520	Manufacture of Drug Substance Aseptic Filling Analytical Testing Manufacture of the Drug Product (filled, unlabeled vials)
Grifols Deutschland GmbH	Lyoner Strasse 15 60528 Frankfurt, Germany	Manufacturer responsible for import into the EU and batch release in the EEA in accordance with Article 40 and Article 51 of Directive 2001/83/EC as amended

Manufacture

The finished product for Human Albumin Solution L/A 25% is defined as the packaged final container.

The sterile albumin solution is aseptically filled into sterile bottles and pasteurized for not less than (NLT) 10 hours and NMT 11 hours at 59.5 to 60.5°C within 24 hours after completion of filling.

The final containers are incubated at 30-32 °C for not less than 14 days or at 20-25 °C for not less than 4 weeks in accordance with requirements in the Ph.Eur. monograph for albumin solutions.

No process validation data has been provided.

It has been confirmed that the acetone-free process is included in the MAA for the EU approved Plasbumin 25% Grifols and also that only plasma included in the EU certified Grifols PMF is used for manufacture also for the acetone-free process. In such case, the absence of process validation data can be accepted.

A nitrosamine risk evaluation was requested as an major objection during assessment. A statement has been provided from Grifols, concluding that there is no indication for nitrosamines generated at any steps of the manufacturing process of Plasbumin 25%, since neither nitrosating nor nitrosatable agents are likely to be present that might lead to a safety concern. In addition, the report from the risk evaluation has also been provided and found acceptable which was sufficient to resolve the major objection.

Specifications
The finished product specification is presented in the table below.

Table 8. Plasbumin 25% Grifols finished product specification

Test	Specification	Reference	Method
N-Acetyl-DL- Tryptophan	0.07 to 0.09 mmol/g protein	Ph. Eur.	IG_MA-000197A_ING
Aluminum	≤ 200 µg/L	Ph. Eur.	IG_MA-000324A_ING
	≤ 100 µg/L*	Grifols	
Appearance	Clear, slightly viscous, pale yellow to amber or green	Ph. Eur.	IG_MA-000003B_ING
Sodium Caprylate	0.07 to 0.09 mmol/g protein	USP	IG_MA-000198A_ING
Citrate	≤ 0.1 mmol/L	Grifols	IG_MA-000750_ING
Fill Volume	Meets minimum fill volume	USP	IG_MA-000115A_ING
Haem (O.D. 403 nm, 1% w/V)	≤ 0.15 A	Ph. Eur.	IG_MA-000006A_ING
pH of 1% Protein Solution	6.7 to 7.3	Ph. Eur.	IG_MA-000004A_ING
Polymers and Aggregates	≤ 5%	Ph. Eur.	IG_MA-000158A_ING
Potassium	≤ 0.05 mmol/g protein	Ph. Eur.	IG_MA-000005A_ING
Prekallikrein Activator (PKA)	≤ 35 IU/mL	Ph. Eur.	IG_MA-000297C_ING
Product Identity (Grabar-Williams)	Main component is albumin	Ph. Eur.	IG_MA-000266A_ING
Total Protein	23.75 to 26.25%	Ph. Eur.	IG_MA-000007A_ING
Purity (AME)	≥ 95% Albumin	Ph. Eur.	IG_MA-000009B_ING
Pyrogen, EP	Must comply	Ph. Eur.	IG_MA-000011A_ING
Sodium	130 to 160 mmol/L	USP (1)	IG_MA-000005A_ING
Sterility	No growth	Ph. Eur.	IG_MA-000012C_ING

(1) Ph. Eur. Specification: Maximum 160 mmol/L

European Pharmacopoeia (Ph. Eur.): The current edition of the European Pharmacopoeia will be used.
United States Pharmacopeia (USP): The current edition of the USP will be used.
*Release requirement

Specifications comply with requirements in European Pharmacopeia monograph for human albumin solution and most of the test methods are performed in accordance with European Pharmacopeia.

Stability

A shelf-life of 36 months when stored at the licensed storage condition of 30°C is claimed. Stability data for batches stored at 30±2°C has been provided for 3 batches stored for 36 months justifying the claimed shelf-life.

2.2.4.4. Adventitious agents' safety

Studies were performed to characterize the scale-down models used to evaluate the virus clearance capacity of the precipitation of Fraction II+III step and the precipitation of Fraction IV step.

Experimental data from these studies demonstrated that these scale-down models are valid representations of the production process. Therefore, the virus removal/inactivation data generated using these models can be considered valid. Since the pasteurization step only requires a water bath for holding the sample at the proper temperature, no scale down model was necessary for the setpoint studies.

A summary of the virus validation studies is provided in the table below:

Table 9. Summary of the virus validation studies

Process Step	Enveloped Viruses			Non-enveloped Viruses		
	HIV-1	BVDV	PRV	Reo3	HAV	PPV
Precipitation of Fraction II+III	3.4	3.5	3.9	≥2.1	1.4	1.0
Precipitation of Fraction IV[a]	≥4.3	≥4.1	≥3.9	≥4.4	3.9	4.6
Pasteurization[b]	≥5.9	≥5.2	≥4.8	5.6	4.4	1.6
Overall Clearance Capacity	**≥13.6**	**≥12.8**	**≥12.6**	**≥12.1**	**9.7**	**7.2**

[a] EMCV was also evaluated for the Precipitation of Fraction IV step. The virus clearance capacity (log_{10}) was 3.7.

[b] WNV was also evaluated for the Pasteurization step. The virus clearance capacity (log_{10}) was ≥6.7.

Sufficiently detailed information has been provided for the virus validation studies.

TSE and prion Safety

Regarding the risk of transmission of transmissible spongiform encephalopathies (TSE) through the use of plasma-derivatives, the safety of the medicinal product is accomplished by the suitability of plasma donors, the use of low-risk raw materials and steps in the manufacturing process that have been shown to achieve TSE clearance.

No animal derived materials are used in the manufacture of Albumin.

2.2.5. For the ancillary medicinal substance as incorporated in the medical device - gentamicin sulfate

Kitazato ART media supplemented with antibiotics are a range of media products designed for use in Assisted Reproduction Technologies (ART). Antibiotics are added to ART media to avoid contamination by micro-organisms. Maintaining sterile conditions is crucial in human ART procedures, since human embryos are replaced into the maternal reproductive tract.

All media containing gentamicin sulfate contains 10 mg/l gentamicin sulfate. The manufacturing processes for the *in vitro* fertilisation media have been satisfactorily described and comply with relevant ISO standards.

The amount of gentamicin sulfate in the cell culture media is determined by an ELISA method at a specification limit of 5 – 15 mg/litre. The method has been described and validated. Besides this, also a test for Minimum Inhibition Concentration (MIC) is performed as part of the incoming inspection for gentamicin sulfate.

Data from stability studies have been provided and show that gentamicin is stable in each medium until the end of shelf life. The absence of stability studies to support the pre-formulation step of subdividing the ancillary substance has been satisfactorily justified.

2.2.6. For the ancillary human blood derivative as incorporated in the medical device – Human albumin solutions

Qualitative and quantitative particulars of the constituents

KITAZATO HSA-containing ART media are aqueous solutions of physiological salts to which nutritional / energy substances and buffer systems are added. To enhance specific properties, some media also

contain cryoprotectants, antibiotics or specific medium supplements (like PVP or hyaluronidase). All KITAZATO HSA-containing ART media are supplemented with Human Albumin Solution 25% from Octapharma or Grifols. The amount is dependent on the type of medium and is ranging from 0.16% to 8% (v/v), corresponding with 0.4 g/l and 20 g/l human serum albumin respectively. The amounts of Human Albumin Solution are based on long term experience in the field.

Detailed composition for all different Kitazato solutions has been provided.

Description of method of manufacture

A flow diagram has been provided illustrating where in the manufacturing process of the media the Human Albumin Solution is incorporated. During the weighing / mixing step, all ingredients are sequentially added to the solution (as indicated on the production forms). The correct amount of Human Albumin Solution is added manually as (one of) the last ingredient(s).

The information provided is in general acceptable considering that the process mainly consists of adding and mixing ingredients into a solution. Information on batch formula and batch size have been provided as requested, indicating the specified amount (volume or weight) of the human albumin solution to be incorporated into the specified amount (volume or weight) of the ART media.

Controls of starting materials

Acceptance criteria applied by the medical device manufacturer have been clearly stated.
These criteria include that CTD module 2.3 and module 3 or mini excipient file are available, that an EMA approved PMF certificate and annual updates are available and that the product has an EC official control authority batch release certificate. Furthermore, there is an expiry date limit for incoming Albumin of not less than 2 years after date of receipt to ensure synchronisation of expiry dates with the medical device. This approach is found acceptable.

Quality agreements have been provided for Plasbumin Grifols to ensure information on updates of certification of the PMF, information on changes to manufacture and control of Albumin considered of relevance to Kitazato, systems for information in case of recalls and systems for traceability from plasma/blood donation to final product of albumin to medical device and vice versa in accordance with EU directives and GMP.

Signed statement is included in the contract between the manufacturer and Octapharma ensuring that:

information on changes to manufacture and control of Albunorm considered of relevance to the will be forwarded, that there is a system for information in case of recalls of the medical product and that there are systems in place for traceability from plasma/blood donation to final product of Albunorm to medical device and vice versa for 30 years, in accordance with EU directives and GMP.

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

Albumin concentration is not tested as in-process control and there are no intermediates in the process that can be tested. This is found acceptable since the albumin concentration is tested on the final medical device solutions.

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

For testing of albumin in the medical device, the following test methods are used:

Qualitative control test:

- Mouse Embryo Assay (MEA)
- Human Sperm Survival Assay (HSSA)/ Sperm Survival Test (SST)

Quantitative test:

- Albumin concentration determination by HPLC-reversed phase

The mouse embryo assay (MEA) is a reliable and acceptable quality system for detecting toxic factors within an embryo culture system. A Human Sperm Survival Assay (HSSA) / Sperm Survival Test (SST) is used for toxicity testing on cell culture media that are intended to be used with human sperm to demonstrate the absence of substances that will reduce the viability of spermatozoa. These tests are general indicator that the quality of albumin does not negatively affect the cells or sperm.

Determination of the exact concentration of human albumin is performed by HPLC-reversed phase.

Description of the test and validation of the HPLC-reversed phase method have been provided. The validation included evaluation of matrix effect of respective ART products on HSA detection and quantification. It was demonstrated that the RP-HPLC method can detect HSA in the range of 0.4-25 mg/ml, without interference of other matrix ingredients. The information provided regarding method description and validation is considered sufficient.

The specifications acceptance criteria for human serum albumin content by RP-HPLC in each media has been provided as requested and is now acceptable.

Stability

Real-time aging and retrospective stability studies have been performed to support shelf life and expiry date claims. Therefore, samples were manufactured at the production facility with the same container/closure system as used with the marketed products. The bottles were stored at the recommended storage conditions.

Besides standard QC tests like pH, osmolality (if applicable), density (if applicable), viscosity (if applicable), endotoxin concentration, gentamicin concentration (if applicable), the following specific tests were included in the stability program to provide evidence that the human albumin solution maintains its desired function throughout shelf-life:

- The mouse embryo assay (MEA).
- Human Sperm Survival Assay (HSSA) are performed on some specific media
- Human albumin concentration - HPLC Reversed Phase:
  determination of the exact concentration of human albumin.

Data from all tests were evaluated against the applicable product specifications at each test interval.

Results support the use of Plasbumin 25% and Albunorm at the currently used concentrations in KITAZATO HSA-containing ART media. Stability data demonstrate that:

- the Plasbumin 25% or Albunorm is stable in each medium until the end of shelf life (up to 18 months shelf life). Also, there was no indication that albumin is degrading into harmful degradation products over time.

- Upon in-use testing (opening of bottles during 7 days for a defined number of times based on the intended use of the medium) and transport stress testing (exposure of medium to higher temperatures, i.e. 5 days at 37°C) the albumin was still stable and there was no indication that albumin is degrading into harmful degradation products over time.

Stability data has been provided for albumin in equivalent Kitazato ART media solutions.

Several stability reports have been provided covering all the solutions listed in the table above.

Shelf-life of Kitazato ART Media was included in the application form and confirmed based on stability studies provided.

The data provided demonstrate that the concentration of albumin is stable within shelf-life. The mouse embryo assay, human sperm survival assay and sperm survival test demonstrate that the albumin does not degrade to such level as to negatively affect the IVF-components.

In general, satisfactory information has been provided in this section with regards to the quality and safety of the albumin as integrated in the medical device.

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

Gentamicin

Overall, there is no significant concern regarding the quality of the gentamicin sulfate ancillary substance given that it is supported by a CEP; R1-CEP 1998-155-Rev 10. Furthermore, the device manufacturer has committed to control the ancillary substance in accordance with the Ph. Eur. and the CEP. The dossier sections relating to the medical device are acceptable.

The major objection raised on nitrosamines risk evaluation has been resolved.

Human Albumin Solution

The two Albumin products used as ancillary substance in Kitazato ART media are Albunorm 250 g/l from Octapharma and Plasbumin 25% from Grifols. Albunorm is approved as medicinal products within EU. Furthermore, all plasma used for manufacture of Albunorm is included in Octapharma PMF. The PMF is certified by EMA and the EU PMF certificate has been provided. All batches of Albunorm included in the Kitazato ART media are subjected to OCABR batch release by EU OMCL laboratory.

It has been confirmed that Plasbumin 25% provided by Grifols is approved within EU and that only plasma included in Grifols' EU certified PMF is used for manufacture. A major objection was raised regarding the manufacturing process used to manufacture the Plasbumin 25% product but this has been resolved and confirmation provided that the process is approved in the EU for the Plasbumin product.

Acceptable nitrosamines risk evaluations have been provided for the albumins from Octapharma and Grifols. The major objections raised on the nitrosamines risk evaluation have been resolved.

For albumin as implemented into the medical device, the information provided is acceptable. Information regarding description of the manufacturing process, specification and acceptance criteria for human albumin included as ancillary substance is acceptable.

Method description and validation data of the test method for determination of Albumin concentration in respective Kitazato IVF solutions have also been provided. The information is acceptable.

Stability data has been provided from studies with solutions stated to be equivalent to the different Kitazato ART media solutions. This approach is acceptable.

It is also proposed to include a recommendation to the Notified Body regarding the overall nitrosamines risk of Kitazato. It is emphasised that the overall risk of nitrosamine impurities is not linked only to ancillary substances and their incorporation and that changes to device processes in the future may modify the risk. It is assumed that the Notified Body has complete oversight on the entirety of the risks (including factors aside from the ancillary substances) and follows up on the evolution of risks during surveillance inspections.

2.3. Non-clinical documentation

Pharmacodynamics

HSA

The role of albumin in cell culture media, embryo handling media and cryopreservative cell culture media is as follows:

- Acts as a chelator to toxic metal ions and metabolic wastes, binding to waste products from cell metabolism and potential contaminants introduced in the media
- Provides colloid osmotic regulation
- Inhibits lipid peroxidation (that can be damaging to sperm cells) by binding hydroperoxy fatty acids
- Acts as a carrier and source of essential molecules needed by the embryo
- Acts as a cryoprotecting macromolecule in cell culture media for cryopreservation of gametes and embryos (reducing physical damage due to freezing/ thawing).
- Has a buffering capacity for small ionic molecules, lipids, and growth promoting substances secreted by the embryo
- Facilitates gamete or embryo manipulation by preventing adsorption to surfaces such as plastic or glass recipients (standard IVF-laboratory equipment) through saturation of the potential binding sites
- Increases medium viscosity, which acts to stabilize cell membranes.

Gentamicin

Gentamicin is an aminoglycoside antibiotic. The antibacterial properties of gentamicin sulfate are believed to result from inhibition of bacterial protein synthesis through irreversible binding of aminoglycosides to the bacterial ribosome, thereby disturbing protein synthesis. The intended action of adding gentamicin sulfate to Kitazato ART media is not to treat a disease, but to avoid the bacterial infection of (sterile) cell cultures during normal handling under strictly hygienic conditions.

Pharmacokinetics

No Pharmacokinetics studies have been performed.

Toxicity

HSA

The applicant has provided with general information retrieved from the Core SmPC for human albumin solution (EMA/CHMP/BPWP/494462/2011 rev.3). Briefly:

- Human albumin is a normal constituent of human plasma and acts like physiological albumin.
- In animals, single dose toxicity testing is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.
- To date, human albumin has not been reported to be associated with embryo-fetal toxicity, oncogenic or mutagenic potential.
- No signs of acute toxicity have been described in animal models.

Since KITAZATO HSA-containing ART media are not intended to be administered to the patient, non-clinical pharmacokinetic studies are therefore not applicable. However, the medical devices which are used during in-vitro fertilization procedures ending in embryo transfer and/or intra-uterine injection (IUI) might come into direct contact with the uterus mucosal membrane (Gamete Buffer, SepaSperm wash) but the exposure can be considered negligible. Typical exposure to the patient is once per menstrual cycle and far less than 300-500 µL medium is used in such procedures. With embryo transfer, embryos are usually aspirated into a catheter, so that the volume to be transferred is 15-20 µL ('The Bourn Hall Guide to Clinical and Laboratory Practice, Textbook of in vitro fertilization and assisted reproduction). Therefore, the maximum level of human albumin solution the patient will be exposed to is < 8 µL or maximally < 20 µL. This corresponds with 2 mg and 5 mg human albumin respectively and does not present any safety concern. Also, the maximum level of exposure is once per menstrual cycle for as only one IUI or ET is performed per cycle.

Gentamicin

The addition of gentamicin into ART culture media devices is intended to work as antimicrobial preservative of the media. Gentamicin is a preservative, used for bacteria growth suppression, popularly used in ART procedures either in veterinary or human studies, without any evidence of gentamicin penetration into oocyte or embryo. Most commercial ART companies provide media with 10 mg/l gentamicin (Quinn 2014).

In analogy with the calculation for HSA above regarding embryo transfer, embryos are usually aspirated into a catheter, so that the volume to be transferred is 15-20 µL. Therefore, the maximum level of gentamicin the patient will be exposed to is < 5 µg and only once per menstrual cycle for embryo transfer and IUI media. Penetration of aminoglycosides into tissues is reported to be less than 20% and quantity in contact with mucosal membrane is less than 5µg. The quantity of gentamicin to be absorbed by uterus mucosa tissues is considered at non-detectable levels and therefore the exposure can be considered negligible.

Use of human serum albumin and gentamicin in Kitazato ART media

The media have been on the market for a long time, and results from numerous mouse embryo assays (MEA) and sperm survival tests (SST) / human sperm survival assays (HSSA) on KITAZATO HSA-containing ART media do not indicate toxicity to gametes/embryos during shelf life. According to the Applicant, the MEA and the HSSA/SST are reliable and acceptable quality tests for detecting toxic factors within an embryo culture system or toxic factors exposed to spermatozoa. The MEA or HSSA/SST will fail in case of toxicity and/or the presence of heavy metals in the medium. In this way, any (gentamicin induced) toxicity for gametes / embryos will be detected. MEA and/or HSSA/SST is performed for each batch before batch release.

Further, the media intended for ET/IUI were evaluated for cytotoxicity potential using a XTT cytotoxicity test (in accordance with ISO 10993-5, Table 3). The tests concluded that the media do not have a cytotoxic potential.

Acute systemic toxicity/subacute systemic toxicity and implantation effects were added in ISO 10993-1:2018 for surface devices with a prolonged contact with mucosal membranes. In theory, to cover these endpoints additional in vivo testing would be required on the media intended for embryo transfer /IUI. However, the manufacturer has evaluated this, and the conclusion of this risk assessment is that no additional testing is needed.

Local tolerance

The majority of KITAZATO HSA-containing ART media only come in direct contact with human gametes / embryos. However, the devices intended for embryo transfer or IUI, i.e. Gamete Buffer media, SepaSperm wash, come into direct contact with mucosal membrane and have therefore been evaluated regarding the irritant and the sensitizing potential in accordance with ISO 10993-1

The results of these tests demonstrated that Kitazato ART media supplemented with antibiotics meet the requirements of the ISO 10993-5 and ISO 10993-10 guidelines.

2.3.1. Discussion and conclusion on the non-clinical documentation

The applicant has adequately described the pharmacodynamic applications of use of human serum albumin and for its incorporation as a medical device in Kitazato ART media. Regarding gentamicin, it is a widely used antibiotic and the antibacterial properties of the substance are considered well-known. The role of the substance in the Kitazato ART media supplemented with HSA and/or gentamicin is to avoid infection of the cell cultures, and the substance is included in other commercially available ART products with the same ancillary function.

No Pharmacokinetics studies have been performed with HSA which is considered acceptable. The product is not intended for administration to the patient, and based on the calculations provided by the Applicant, the exposure from the medical devices which are intended for embryo transfer and/or intra-uterine injection (IUI), which might come into direct contact with the uterus mucosal membrane (Gamete Buffer, SepaSperm wash) will be minimal and of no pharmacokinetic relevance.

The Core SmPC for Human Albumin Solution (EMA/CHMP/BPWP/494462/2011 rev.3) reviews a number of aspects relevant for toxicity for Human Albumin. Human albumin is a normal constituent of human plasma and acts like physiological albumin. Animal studies have revealed little relevance in single-dose studies; no signs of acute toxicity are observed, and these studies do not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated dose toxicity studies are impracticable, due to the development of antibodies to heterologous protein in animal models. Human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.

Theoretical calculations provided by the Applicant support that the maternal exposure levels to HSA and gentamicin are very low (2-5mg HSA and less than 5µg of gentamicin per treatment cycle), which supports the safe use of the ancillary substances in the Kitazato products. For reference, the SmPC for Gentamicin Panpharma 40 mg/ml, suggests dosing in adults of 3-6 mg/kg/day for the treatment of infections.

The Applicant reports data from batch release testing where the Mouse Embryo Assay and Human Sperm Survival Assay (HSSA) / Sperm Survival Test (SST) have been used for quality control of the media batches. These data and the long-term clinical use of the media support the safe use of the products. One non-confirming product due to failed HEA/HSSA/SST test (Error! Reference source not found.) was reported. However, a negative result in the MEA/HSSA/SST tests will not necessarily relate to the ancillary substances as variations in other parts of the media composition may also have impacted on the result. There is no need for further in vivo animal studies with human albumin or gentamicin.

No new studies have been provided regarding genotoxicity, carcinogenicity or reproductive toxicity. This is considered acceptable. The ancillary substances used are approved medical products and considered well-known from a toxicological perspective, consequently no such studies are considered needed. The local tolerance and biocompatibility has been evaluated for the solutions which come into contact with mucosal membranes. These studies were performed in accordance with the relevant ISO standards. The conclusion from the studies that the Kitazato ART media meet the requirements of the ISO 10993-5 and ISO 10993-10 guidelines.

To conclude, from a non-clinical point of view, the use of HSA and gentamicin in the Kitazato ART media is considered acceptable.

2.4. Clinical evaluation

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

Kitazato ART media is intended for use in assisted reproductive procedures, which include gamete and embryo manipulation and is a protein supplement for culture medium.

Historically, embryo culture media, as well as other types of media used in IVF procedures, have been extensively supplemented with protein in the form of serum albumin. The inclusion of protein in the media is generally believed to be important. Endogenous albumin is the most abundant protein in the female reproductive tract and is believed to be important in maintaining embryo physiology.

Human serum albumin (HSA) is used as a protein supplement in the medical device, intended to serve a number of functions such as a surfactant preventing the embryo from sticking to dishes and pipettes, a chelating agent against potential toxins, a nutritive source for the embryo, a pH buffer and mediating capacitation of spermatozoa in vitro. It is generally viewed that the culture media supplemented with HSA is beneficial when culturing human embryos and that its use has been shown to increase pregnancy outcome.

The culture media for assisted reproductive procedures are intended to be used sequentially and have been developed to meet the changing need of the embryo during the in-vitro culture period and to minimize intracellular stress. Compared to older versions of media, the current media have more optimized amino acid and vitamin compositions, and the different solutions all have the same ionic backbone which gives similar pH and osmolality in the different media.

The safety and effect or usefulness of HSA-solution are assessed by review and evaluation of available published data for the culture media for assisted reproductive procedures. Data from the studies have also been submitted. From the review reports and data submitted, the links between the scientific literature and the claimed attributes of HSA could be demonstrated.

Gentamicin sulfate is also included in all Kitazato ART media as ancillary medicinal substance. Gentamicin is an aminoglycoside antibiotic. The intended action of adding gentamicin sulfate to

Kitazato ART media is not to treat a disease, but to avoid the bacterial infection of (sterile) cell cultures during normal handling under strictly hygienic conditions.

In conclusion, the applicant has adequately described the pharmacodynamic applications of use of human serum albumin and for its incorporation as an ancillary human blood derivative in KITAZATO HSA containing ART media. Gentamicin is a widely used antibiotic and the antibacterial properties of the substance are considered well-known. The role of the substance in the Kitazato ART media is to avoid infection of the cell cultures.

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

The major drawbacks of using HSA in the media are the possible risks of transmitting viral/prion contaminations, the lot-to-lot variability and presence of impurities due to different contamination levels of fatty acids and other small molecules. The risk for transmission of viral/prion related diseases is considered by the Applicant to be extremely remote due to the effective donor screening, selection, and a pasteurization procedure during the HSA manufacturing process and the small (<20µl) amount of HSA to which the patient is exposed during embryo transfer.

There are no new safety issues identified with the known constituent's human serum albumin and gentamycin in the culture media.

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

The discussions provided by both the medical device manufacturer and Notified Body on albumin's physiological roles and the established use of serum albumin supplementation of ART media, in addition to the literature evidence provided by the medical device manufacturer, sufficiently demonstrate the usefulness of HSA added to the ART media. Further, the Medical Device Manufacturer has 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 are considered to be low. This is supported by further submissions from the manufacturer detailing a log reduction in viral particles during the manufacturing process.

In conclusion, the clinical benefit/risk profile of the ancillary medicinal substances (human serum albumin and gentamicin) incorporated in the medical device is assessed as positive.

2.4.4. Discussion and conclusion on the clinical evaluation

The established practice of serum albumin supplementation of ART media is well recognised and widely accepted and has been shown by the medical device manufacturer to be compatible with average or above average rates of embryo and blastocyst survival, blastocyst implantation, clinical pregnancy, and live births in humans. Discussions were provided by both the medical device manufacturer and Notified Body 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.

The role of gentamicin in the Kitazato ART media is to avoid infection of the cell cultures. Taken together, the discussions, submitted literature and record of historical practice sufficiently demonstrated the usefulness of HSA and gentamicin added to the ART media.

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, the product labelling should contain information outlining these risks.

Overall, the clinical benefit-risk balance for this product is positive and the application could be approvable.

2.5. Overall conclusions

The information provided on Albunorm 250 g/l itself is considered acceptable.

The information provided on Plasbumin 25% Grifols itself is considered acceptable. It has been confirmed that Plasbumin 25% provided by Grifols is approved within EU and that only plasma included in Grifols' EU certified PMF is used for manufacture.

The information provided on gentamicin sulfate is considered acceptable.

For albumin and gentamicin as incorporated into the medical device, the information provided is acceptable.

The application is recommended for approval from a quality, non-clinical and clinical point of view.

2.6. Recommendation

Based on the CHMP review of data submitted, the CHMP considered by consensus decision that the quality and safety including the benefit risk profile of human albumin solution / gentamicin sulfate used as ancillary medicinal substance(s) in the Kitazato ART media was favourable and therefore granted a positive opinion in the consultation procedure.