CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212279Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To:	NDA 212279
From:	Rajan Pragani, Ph.D., Senior Chemist, Office of New Drug Products (ONDP) Norman R. Schmuff, Ph.D., Associate Director for Science, Office of Process and Facilities (OPF)
Date:	11/7/2019
Subject:	ExEm Foam – Agency Determination of Active Ingredient and Established Name

I. SUMMARY

This memo provides the Agency's active ingredient determination for the drug product ExEm Foam (new drug application (NDA) 212279). ExEm Foam is a water-soluble ultrasound contrast agent (UCA) prepared by mixing one syringe of sterile Gel (hydroxyethyl cellulose, glycerin, and purified water) and one syringe of sterile purified water immediately prior to use. After deliberations between Agency components (Office of Pharmaceutical Quality (OPQ), Office of New Drugs (OND), and the CDER Exclusivity Board (Exclusivity Board)) it was decided that the active ingredient in ExEm Foam is the "bubbles" formed when the contents of the two syringes (gel and sterile purified water) are mixed. These bubbles comprise the gas, and the bubble wall, including all the components that make up the bubble wall. It was also decided to name this active ingredient "air polymer-type A" to reflect the components of the bubble (air and the components that comprise the bubble wall)[1] and that the established name be "(air polymer-type A) intrauterine foam."

The Agency's reasoning is provided below.

I. BACKGROUND

NDA 212279 for ExEm Foam was initially submitted on October 9, 2018. ExEm Foam is an ultrasound contrast agent (UCA) indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility.

ExEm Foam is provided to the user for preparation as a single-dose kit containing: 5 milliliter (mL) sterile clear gel [polymer-type A (80.97 mg hydroxyethyl cellulose), 434.80 milligram (mg) glycerin 85%, and purified water] with a pH of 6 to 7.5; and 5 mL

[1] Hydroxyethyl cellulose (b) (4); glycerin and water (b) (4)

sterile purified water with a pH of 6 to 7.5. Both the gel and the sterile purified water are provided in separate syringes. The kit also contains a coupling device (Combifix Adapter).

Prior to use, the syringes are connected to each other through the coupling device, then their plungers are pushed back and forth at least 10 times so as to mix the contents of both syringes to create approximately 10 mL of ExEm Foam. ExEm Foam upon preparation is a milky-white, water-soluble foam with an osmolality of approximately 462 mOsm containing between 10,000 to 127,000 bubbles per mL with a median size of 45.6 to 60.6 micrometers (for bubbles between 20 to 200 micrometers).

The intrauterine administration of the drug product is conducted by catheter, and must be done within 5 minutes of preparation to ensure adequate imaging. When ExEm Foam is administered, the bubble containing foam is deposited inside the uterus and travels through the fallopian tubes. The foam acts to open the fallopian tubes from their naturally collapsed state by physically occupying space as the foam expands, after which sonography is performed to determine if the foam flowed the length of the fallopian tubes. If there is a blockage, the foam will not flow the length of the fallopian tubes. The bubbles in the foam possesses "echogenic" properties, a characteristic relevant to use in imaging via ultrasound. Specifically, the bubbles within the foam are echogenic meaning that they reflect ultrasound waves to produce ultrasound echoes. During the ExEm Foam diagnostic procedure, ultrasound waves sent by the transducer are reflected back as ultrasound echoes to the transducer for detection. The detected ultrasound echoes are transformed into a sonogram image for clinical diagnosis of fallopian tube patency.[2]

(b) (4)

On July 30, 2015, the Office of Combination Products (OCP) concluded that ExEm Foam is a combination product, and that because its primary mode of action is attributable to the UCA, it should be regulated as a drug by

[2] See ExEm Foam Label Section 2.4 (Imaging Guidance). "A fallopian tube is classified as patent if ExEm Foam is observed to pass from the tube and spill into the peritoneal cavity… A fallopian tube is classified as occluded if ExEm Foam is not observed to pass from the tube and spill in to the peritoneal cavity. As secondary findings, (1) there may be no bright line due to no flow into the fallopian tube, or (2) the tubal lumen may appear distended and contrast flow might be observed only in the intramural or isthmic part of the tube."

(b) (4)

CDER.[4] (b) (4) [redacted]

Following this decision, Giskit B.V. submitted an NDA for ExEm Foam.[6] In its application, Giskit B.V. did not, however, identify an active ingredient.[7] Following initial review of the application FDA sent an information request (IR) to the applicant on December 21, 2018, asking it to "[p]rovide and justify an established [non-proprietary] name for the proposed drug product as required by 21 CFR 299.4." The Agency stated that '[t]he established name must contain the [active component(s) of the drug] and [dosage form], for example, "active ingredient(s) intrauterine foam."[8] The Division received a first response to this IR on January 25, 2019, in which the applicant provided the established name (b) (4) [redacted]

FDA sent Giskit B.V. a revised request on February 26, 2019,[10] in which the Agency asked that Giskit B.V. "[r]evise … [its] drug product name (b) (4) [redacted]

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[4] UCAs have been regulated as drugs by CDER since the decision in *Bracco Diagnostics, Inc. v. Shala/a* (963 F. Supp. 20 (D.D.C 1997)).

(b) (4) [redacted]

[6] Giskit B.V. first used the proprietary name ExEm Foam in its NDA.

[7] Giskit B.V. stated that (b) (4) [redacted] has no active pharmaceutical ingredient. Pharmaceutical Development (b) (4) [redacted] submitted by Giskit B.V., p. 4, Oct. 9, 2018. (b) (4) [redacted]

[8] See Request for Information (Dec. 21, 2018).

(b) (4) [redacted]

[10] See Request for Information (Feb. 26, 2019).

and asked that the applicant [redacted] in the drug product name," and "[i]nclude the dosage form, i.e., "foam." In a response dated March 14, 2019, Giskit B.V. provided the established name, [redacted][11] In identifying the established name in this manner, the applicant stated that the name should convey, i.e., (a) the route of administration (intrauterine), (b) the dosage form (foam) and [redacted]

The Agency engaged in further internal discussions between various Agency components (OPQ, OND, and the Exclusivity Board, among others) to seek scientific and regulatory concurrence on how best to characterize the active ingredient for this product.

In determining the active ingredient, the Agency looked to the definition of "active ingredient" in 21 CFR 314.3, Agency precedent with respect to UCAs, and input from subject matter experts from OPQ and OND. Each of these considerations is discussed below.

II. ANALYSIS

A. Relevant Statutory and Regulatory Provisions

FDA's regulations define "active ingredient" to mean:

> "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the

[11] Response to FDA Request for Information (Mar. 14, 2019).

[12] Id.

[13] Id.

> manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."[14]

With regard to naming ingredients, section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) generally requires the label of a drug product to bear the established name of the drug product's active and inactive ingredients as follows:

> (A) the applicable official name designated pursuant to section 508 [of the FD&C Act],or (B) if there is no such name and such drug, or such ingredient, is an article recognized in an official compendium, then the official title thereof in such compendium, or (C) if neither clause (A) nor clause (B) of this subparagraph applies, then the common or usual name, if any, of such drug or of such ingredient . . . .[15]

The United States Pharmacopoeia (USP) is one of the official compendia recognized in the FD&C Act (*see* section 201(j) of the FD&C Act). Section 508 of the FD&C Act (21 U.S.C. 358) authorizes the Agency to designate an official name for any drug if the Agency determines "that such action is necessary or desirable in the interest of usefulness and simplicity." In the absence of designation by FDA of an official name, the current compendial name will ordinarily be used as the established name. If there is no compendial name, the common and usual name would generally be considered to be the established name. FDA's general policy on established names is set forth in 21 CFR 299.4. With respect to UCAs, the Agency's practice is to generally require that the established name identify the gas and shell, route of administration (if applicable), and dosage form.

B. Agency Policy on UCAs

The FDA has previously approved several UCAs whose echogenic properties are derived from the presence of microspheres or bubbles in the administered drug product but has not previously articulated a framework by which the active ingredient for these products is determined. Some of these UCAs are discussed below.[16]

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[14] 21 CFR 314.3(b).

[15] Section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[16] We note that ExEm Foam is indicated for the diagnosis of fallopian tube patency, while the other UCAs (Albunex, Optison, Definity, and Lumason are indicated for IV delivery for cardiac imaging (and some are used to image other parts of the body, as well). ExEm Foam is the only foam product; the other UCAs are liquid suspensions for IV delivery.

In 1994, the Agency approved Albunex (albumin (human) 5%, sonicated), a UCA for use in echocardiography and other ultrasound radiology procedures prepared by sonicating 5% human serum albumin to produce stable, air-filled microspheres encapsulated by a shell of aggregated albumin.[17] The air-filled microspheres have characteristics similar to those of air bubbles in water, with respect to both backscatter and attenuation of the ultrasound signal. The active ingredient identified in the labeling for Albunex (and as reflected in the established name) is human albumin.[18]

Subsequently in 1997, the Agency approved another human albumin containing UCA, Optison (perflutren protein-type A microspheres) injectable suspension (NDA 020899), for intravenous use.[19] The microspheres in Optison which are responsible for the echogenic contrast effect of the product are comprised of human albumin shells surrounding perflutren (octafluoropropane) gas.[20] The Optison microspheres are responsible for the echogenic contrast effect of the product. In its NDA, the Optison sponsor identified the active ingredient as human albumin[21], as does the Orange Book.[22]

Following the approval of Optison in 1997, the Agency approved another perflutren gas-containing UCA when it approved Definity (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use (NDA 021064).[23] The Definity product consists of a vial whose components (perflutren gas, lipid, and other components) upon activation by shaking with a modified dental amalgamator yields an injectable suspension of perflutren

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[17] Albunex was first approved under PMA P900059 as a device. Use of Albunex was extended in 1997 via a PMA supplement to the assessment of fallopian tube patency in combination with ultrasound imaging. Although Albunex was one of the products initially regulated by the agency as a device, the Agency in response to *Bracco Diagnostics, Inc. v. Shalala* (963 F. Supp. 20 (D.D.C 1997)), and related citizen petitions determined that contrast agents should be regulated as a drug.

[18] A review of the administrative record related to Albunex does not reveal why the active ingredient for Albunex was identified as human albumin. However, this decision appears reasonable given that human albumin is the primary component of this product (specifically the walls of the microspheres responsible for the echogenic properties of the product).

[19] Optison is approved for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders.

[20] Human albumin within the microsphere shell makes up approximately 5-7% (w/w) of the total human albumin in Optison prior to administering it to the patient.

[21] More specifically, the NDA identifies the active ingredient as (human albumin) (b) (4) USP.

[22] Recent discussions by the Biosimilar Policy Council on 6/11/19 related to certain "transition products," indicate that Optison would continue to be approved under an NDA.

[23] Definity is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

lipid microspheres. The perflutren lipid microspheres are composed of perflutren gas encapsulated in a shell comprising mostly lipids and a polymeric component (e.g., MPEG5000 DPPE). The Agency's Chemistry, Manufacturing, and Controls (CMC) review for Definity does not explicitly identify the active ingredient, but addresses review of the "components" — perflutren gas and lipids —that upon activation provide the perflutren lipid microspheres. The Orange Book lists the active ingredient in Definity as perflutren. Definity's established name — Perflutren Lipid Microsphere — was provided by the applicant in its NDA.

In 2014, FDA approved a sulfur hexafluoride (SF_6) gas-containing microsphere UCA product when it approved NDA 203684 for Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use.[24] LumaSon is provided as a single-patient use kit in which a vial containing a lyophilized lipid is combined with SF_6 gas and diluent .9% Sodium Chloride Injection. When combined, the resulting product is a milky white, homogeneous suspension containing SF_6 lipid-type A microspheres. The SF_6 lipid microspheres are composed of SF_6 gas in the core surrounded by an outer shell monolayer of phospholipids. The NDA as submitted and initial reviews identified the active ingredient as (b) (4) with the strength of the product expressed as the number of microspheres per mL.[25] However, the proposed name of the active ingredient was changed to "sulfur hexafluoride lipid-Type A microsphere" during the pendency of the review and prior to approval.[26]

The Cross Discipline Team Leader (CDTL) review for Lumason states that the "[t]he drug substance consists of sulfur hexafluoride (SF_6) gas in the core surrounded by an outer shell monolayer with two kinds of phospholipids. The microspheres are composed of the drug substance with palmitic acid as a stabilizer and polyethylene glycol as a (b) (4)."[27] This nomenclature is reflected in the CMC review for NDA 203684 which identifies Lumason with the established name "Sulfur Hexafluoride Lipid-Type A Microsphere" with SF_6 gas as the microsphere core component, and the phospholipids (1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and 1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na)) and hexadecenoic

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[24] In 2014, Lumason was approved for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Since then it has also been approved for ultrasonography uses.

[25] See for example, NDA 203684, Lumason, Label, Labeling & Packaging Review (Aug. 8, 2012). The strength of the product in contemporary labeling and reviews continues to be expressed as such.

[26] A review of all documents in the administrative record for this NDA do not indicate why this change was made. Discussions with the reviewing Division, however, indicate that the term "Lipid Type A" was used to cover the composition of lipids seen in Lumason.

[27] NDA 203684, Lumason, CDTL Review (Sep. 14, 2012), at 3.

acid (palmitic acid), a stabilizer, as the microsphere shell components.[28] The Orange Book identifies the active ingredient as Sulfur Hexafluoride Lipid-Type A Microsphere.

B. Active Ingredient Analysis for ExEm Foam

As noted above, the Agency's analysis and determination of the active ingredient for ExEm Foam was made on the basis of the regulatory definition of active ingredient in 21 CFR 314.3(b), a review of Agency precedent and policy regarding active ingredient identity for certain UCAs, and discussions with Agency subject matter experts in OPQ, OND, and the Exclusivity Board.

"Active ingredient" is defined in relevant part as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals."[29] As an initial matter, therefore, the Agency must look to the indication for which ExEm Foam is being approved to determine which of the activities provided in the above regulatory definition are relevant.

ExEm Foam is indicated for the diagnosis of fallopian tube patency in women with known or suspected infertility. Therefore, in determining the active ingredient for ExEm Foam, the Agency focused on determining which component or components had a "direct effect in the diagnosis… of disease," in this instance.

The ExEm Foam is transferred into the fallopian tubes where it acts as a distension medium to open the fallopian tubes from their natural collapsed state. If the fallopian tube is patent (open) the foam will flow through and fill the fallopian tube; if it is non-patent (truly obstructed) the foam will not flow the length of the tube. As a UCA,[30] the bubbles in ExEm Foam have echogenic properties that allow these bubbles to resonate or reflect in response to ultrasound in a manner that allows them to stand out from the surrounding medium, thus creating an image allow assessment of whether the fallopian tubes are open (patent) or closed by showing where the flow of foam stopped on the image.

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[28] NDA 203684, Lumason, CMC Review (Sep. 16, 2014), generally.

[29] 21 CFR 314.3(b)

[30] As defined in FDA's *Guidance for Industry: Developing Medical Imaging Drug and Biological Products, Part 1: Conducting Safety Assessments* (2004), "A contrast agent is a medical imaging agent used to improve the visualization of tissues, organs, and physiologic processes by increasing the relative difference of imaging signal intensities in adjacent regions of the body." An ultrasound contrast agent is a type of contrast agent intended to reflect sound waves in response to ultrasound in a manner that allows the agent to stand out from the surrounding medium (e.g., surrounding blood and tissues in the body).

Based on a review of the product application, and discussions with subject matter experts in OND and OPQ, it was determined that the bubbles in the foam achieve its direct effect in the diagnosis of fallopian tube patency in women with known or suspected infertility, and not by any of the individual components (air, water, hydroxyethyl cellulose, and glycerin) alone. More specifically, it was determined that bubbles in the foam (comprising the gas (air) inside the bubble, and the bubble wall) are the active ingredient because the bubbles in their entirety provide a "direct effect in the diagnosis" of fallopian tube patency.

Consequently, FDA determined that the established name deemed appropriate for ExEm Foam should be (air polymer-type A) intrauterine foam. Unlike the established names proposed by the applicant (b) (4) , this name indicates that the active ingredient is "air polymer type A," a name that reflects the components of the bubbles — air and "polymer-type A," a term that recognizes the polymeric composition of the bubble wall.[31] The Agency informed Giskit B.V. of this determination on September 17, 2019.

The interface between the air within the ExEm Foam bubble and the bubble wall is a critical factor in enabling ExEm Foam's diagnostic function. Specifically, ExEm Foam acts as positive contrast agent and is seen on ultrasound as a highly-resolved white line in the fallopian tube. The highly-resolved white line originates from the consistent reflection of ultrasound waves by the product's air/bubble wall interfaces found in the fallopian tube.[32] Thus, both the bubble walls and the gas within the bubbles in ExEm Foam are essential to the efficacy of the product as a positive contrast agent. Further, the Agency determined that the name "air polymer-type A" was more consistent with precedent set by established names of recently approved UCAs (for example, Lumason).

It is important to note that air alone would not be useful for fallopian tube imaging due to interference from image artifacts. When air alone is imaged on ultrasound, image artifacts, such as ring-down artifact, comet-tail artifact, and dirty shadowing,[33] usually

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[31] FDA followed the format for naming the component(s) of the shell similar to other UCAs (e.g. protein-type A and lipid-type A) for ExEm Foam because it also contains a large molecule (hydroxyethyl cellulose, a polymer).

[32] In the labeling, ExEm Foam is described as containing between 10,000 to 127,000 bubbles per mL. Each air bubble provides an air-bubble interface that can produce an ultrasound echo. The accumulated effect of several thousands of echoes is the production of a highly-resolved white line image in the fallopian tube on ultrasound.

[33] Hindi A, Peterson C, Barr RG. "Artifacts in diagnostic ultrasound." Reports in Medical Imaging 2013:6 29-48.

occur because irregular ultrasound echoes are produced by reflection from unusual interfaces in the body (which is in contrast to generating consistent ultrasound echoes from regular air-bubble wall interfaces).[34] The injection of air alone[35] into the fallopian tubes would not enable consistent visualization of peritoneal spillage out of the fallopian tubes because these image artifacts would likely obscure the image to prevent diagnosis. Because visualization of peritoneal spillage is the major determinant for diagnosis of fallopian tube patency, air alone would not be useful as a positive contrast agent.

Furthermore, each individual non-gas component in ExEm Foam would not independently function as a positive contrast agent. Instead, each of these components would provide negative contrast [36] on ultrasound[37] because of the absence of gas bubbles. To form a positive contrast agent from, for example, hydroxyethyl cellulose, gas must be introduced in the form of a gas bubble (which is capable of producing ultrasound echoes). Thus, both the gas and the bubble wall in ExEm Foam are considered essential for the product's appearance on ultrasound (as a positive contrast agent) and for the product's intended effect, i.e., the visualization of fallopian tube patency.

The exact composition of the bubble wall (which differs from the internal gas core and the mixture external to the bubble wall) cannot be defined and quantified by current analytical techniques.[38] It is this wall, regardless of its exact composition, and the air

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[34] Due to these image artifacts, the tissues and anatomic structures located deep behind the air are usually obscured. The obscuration of the pancreas from sonographic visualization due to air in the overlying stomach or small bowel is a frequently encountered example of physiologic air impeding sonographic imaging in clinical practice. In typical ultrasound imaging of organs, physiological gas often creates reverberation artifacts that obscure organ architecture. For an example, see: "Detection of intraperitoneal free gas by ultrasound." AJUM May 2013 16 (2) 56-61.

[35] Injection of air alone for fallopian tube ultrasound imaging is not used in clinical practice.

[36] Visualization of the normal fallopian tubes is more difficult with a negative contrast agent, although not impossible, as earlier techniques of diagnosing fallopian tube patency with ultrasound used negative contrast agents such as saline for diagnosis. See: Boudghene FP, Bazot M, Robert Y, Perrot N, Rocourt N, Antoine JM, Morris H, Leroy JL, Uzan S, Bigot JM. "Assessment of Fallopian tube patency by HyCoSy: comparison of a positive contrast agent with saline solution." Ultrasound Obstet Gynecol 2001; 18: 525–530.

[37] Water, saline, and ultrasound coupling gel appear black on ultrasound.

[38] From a chemistry perspective, current analytical methods are not capable of defining and quantifying the exact composition of the bubble wall alone within the ExEm Foam mixture. Analytical methods used to characterize bubble wall composition include (but are not limited to) cryo-scanning electron microscopy (cryo-SEM), high-resolution optical microscopy, and transmission electron microscopy (TEM). See Jingam Park, Donghee Park, Unchul Shin, Sanghyub Moon, Chihyun Kim, Han Sung Kim, Hyunjin Park, Kiju Choi, Bong-Kwang Jung, Jaemin Oh, Jongbum Seo. "Synthesis of Laboratory Ultrasound Contrast Agents." Molecules 2013, 18, 13078-13095. These methods only provide a macroscopic visualization of the bubble wall and do not have the capability to define and quantify the chemical composition of the

within the bubble that are needed, together, to create a clinically useful image. For those reasons, the bubble as a whole has a direct effect on the ultrasound-based diagnosis of fallopian tube patency and thus is the active ingredient in this instance.

With regard to Agency precedent on identifying the active ingredient in UCAs, it is noted that identifying the active ingredient in ExEm Foam as described above is consistent with recent Agency practice, specifically with regard to the Agency's determination of the active ingredient for Lumason (Sulfur Hexafluoride Lipid-Type A Microsphere). Although ExEm Foam and Lumason are approved for different indications (the diagnosis of fallopian tube patency for the former, cardiac imaging for the latter) and are presented in different dosage forms for different routes of administration (ExEm Foam is the only UCA in foam form and is indicated for intrauterine administration, whereas Lumason is a liquid suspension for IV delivery), it is the microspheres in Lumason and the bubbles in ExEm Foam that are responsible for the echogenic properties that in turn allow for the diagnostic uses of both drug products.

Moreover, although the active ingredient in both Albunex and Optison is listed as human albumin,[39] the administrative records for each of these products indicate that, in both cases, the sponsor and the Agency recognized during review that the microspheres formed upon combination of the albumin and gas (air or perflutren) were combined were responsible for the echogenic properties of the product.[40] Similarly, the administrative record for Definity suggests that despite listing the active ingredient as perflutren gas, the Agency approved the product with an established name that reflected the microsphere character of the product ("perflutren lipid microspheres") as well as its principal components, the perflutren gas and the lipid components of the microsphere wall.

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bubble wall. For example, a polymeric bubble wall can be visually differentiated from the internal gas core and the external mixture using microscopy; however, individual molecules in the bubble wall cannot be resolved for identification and quantification. Other non-microscopy analytical methods typically used to characterize ultrasound contrast agents also do not have the capability to define and quantify the chemical composition of the bubble wall alone. Other non-microscopy methods (e.g., laser diffraction, Coulter counter technique, electro-impedance volumetric zone-sensing) used to characterize ultrasound contrast agents address particle size and do not identify chemical components. Furthermore, chromatography (e.g., HPLC, GC, TLC, etc.) can be used to quantify mixtures; however, a chemical derivation or separation step of the bubble wall from the rest of the mixture is typically needed. As these types of steps often alter the composition of the original mixture, a chromatographic analysis may not provide an accurate assessment of the bubble wall composition.

[39] The administrative record does not explicitly identify reasons for these determinations. However, we note that the applicant proposed human albumin as the active ingredient in both products in their respective NDAs, and that the Agency did not challenge this assertion at the time.

[40] While the Orange Book lists human albumin as the active ingredient of Optison, the established name is "perflutren protein-type A microspheres." Optison label, revised Sept. 2016. Accessible at https://www.accessdata.fda.gov/scripts/cder/daf/

III. CONCLUSION

The active ingredient in ExEm Foam is air polymer-type A as described herein.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAJAN PRAGANI
11/07/2019 04:11:10 PM

NORMAN R SCHMUFF
11/07/2019 04:17:02 PM

ADDENDUM

From:	Danae D. Christodoulou, Ph.D., Branch Chief, ONDP
To:	NDA 212279, ExEm Foam
Subject:	Addendum to OPQ integrated Quality Assessment - Drug Product
Applicant:	Giskit B.V.
Date:	11/6/2019

Clarification – Reiteration re. active ingredient and established name

Refer to the active ingredient and established name, "air polymer type A intrauterine foam". The drug product (foam) comprises of echogenic "bubbles" that contain the gas air in the bubble wall with main component the polymer type A (hydrxyethylcellulose), and glycerin (glycerol) and water (b) (4).

Refer to the OPQ Integrated Quality Assessment (IQA) in DARRTS, dated 11/6/2019.
Executive Summary, p. 1
The active ingredient and the established name for the drug product were discussed with the Exclusivity Board, Office of Policy Pharmaceutical Quality (OPPQ), the clinical team (OND) and DMEPA reviewers. After several rounds of discussion, it was concluded that the active ingredient present in the foam consists of "bubbles" that contain air in a shell of hydroxyethyl cellulose, water, glycerol. Hence, the finalized established name for the ExEm Foam is "air polymer-type A". Consider the main component in the shell wall as hydroxyethylcellulose (HEC) with glycerol and water (b) (4) of the formulation. Precedence for designation of the active ingredient and established name are the approved Ultrasound Contrast Agents (UCAs) Albunex, Definity, Optison and Lumason.

Drug Product Assessment, p. 4
Reviewers Evaluation: The active ingredient and the established name for the drug product were discussed with the Exclusivity Board, Office of Policy Pharmaceutical Quality (OPPQ), the clinical team (OND) and DMEPA reviewers. After several rounds of discussion, it was concluded that the active ingredient present in the foam consists of "bubbles" that contain air in a shell of hydroxyethyl cellulose, water, glycerol. Hence, the finalized established name for the ExEm Foam is "air polymer-type A". Consider the main component in the shell wall as hydroxyethylcellulose (HEC) with glycerol and water (b) (4) of the formulation. Precedence for designation of the active ingredient and established name are the approved Ultrasound Contrast Agents (UCAs) Albunex, Definity, Optison and Lumason.

The clarification sentence in red, *"Consider the main component in the shell wall as hydroxyethylcellulose (HEC) with glycerol and water (b) (4) of the formulation"* is added with this addendum. The established name is consistent with product labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANAE D CHRISTODOULOU
11/06/2019 05:26:58 PM

DHANALAKSHMI KASI
11/06/2019 06:35:07 PM
Application Technical Lead

Recommendation: APPROVAL

NDA 212279

Review # 1

Drug Name/Dosage Form	ExEm Foam/ Foam
Strength	10,000 – 127,000 bubbles/mL, median size of 45.6 - 60.6 micrometers for bubbles between 20 – 200 micrometers.
Route of Administration	Intrauterine infusion
Rx/OTC Dispensed	Rx
Applicant	GISKIT B.V.

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	10/09/2018
Quality Response to Information Request	01/25/2019
Proprietary Name/Request for Review	02/08/2019
Quality Response to Information Request	03/14/2019
Quality Response to Information Request	04/08/2019
Quality Response to Information Request	04/15/2019
Quality Response to Information Request	05/23/2019
Quality Response to Information Request	06/05/2019
Quality Information	06/07/2019
Quality Response to Information Request	06/20/2019
Quality Response to Information Request	07/03/2019
Quality Information	07/18/2019
Quality Response to Information Request	08/02/2019
Quality Response to Information Request	09/05/2019
Proprietary Name/Amendment	09/24/2019
Labeling Response	09/24/2019
Quality Response to Information Request	10/03/2019
Quality Response to Information Request	10/10/2019

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Product	Dhanalakshmi Kasi	Danae Christodoulou
Process/Facility	Laurie Nelson	Yubing Tang/Vidya Pai
Microbiology	Maritere Carattini	John Metcalfe
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Dhanalakshmi Kasi	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs: None**

B. Other Documents: None

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The final OPQ recommendation is for Approval.

II. Summary of Quality Assessments

NDA 212279 is a 505(b)(2) application based on literature data without any clinical study reports. [redacted] (b) (4). The drug product was developed to visualize tubal patency in women of low risk of tubal disease. Ex Em gel and water has been marketed in Europe since 2014 as a medical device (see CDTL's review). The drug product (foam) is intended for intrauterine administration and ultrasound imaging.

The ExEm foam kit consists of sterile 11-mL syringe containing 5 mL of gel, sterile 11-mL syringe containing 5 mL of sterile water, sterile coupling device. ExEm foam is prepared by mixing gel and water prior to administration. The Ex Em gel formulation contains glycerol, hydroxyethyl cellulose, and water as ingredients. The applicant did not identify the active ingredients present in the drug product in the original NDA submission. Also, the established name for the drug product was not provided by the applicant. In the 74-day letter the applicant was asked to identify the active ingredients and provide an established name. The active ingredient and the established name for the drug product were discussed with the Exclusivity Board, Office of Policy Pharmaceutical Quality (OPPQ), the clinical team (OND) and DMEPA reviewers. After several rounds of discussion, it was concluded that the active ingredient present in the foam consists of "bubbles" that contain air in a shell of hydroxyethyl cellulose, water, glycerol. Hence, the finalized established name for the ExEm Foam is "air polymer-type A". Precedence for designation of the active ingredient and established name are the approved Ultrasound Contrast Agents (UCAs) Albunex, Definity, Optison and Lumason.

The image quality and ultrasound contrast depend on bubble concentration. Testing of the foam for bubble size and concentration (number of bubbles/ml) is considered as the critical quality attribute and incorporated in the release specification of the foam. The foam is tested by Coulter counter method and the established test limits for foam concentration and size are [redacted] (b) (4) bubbles/mL with the median size of [redacted] (b) (4) micrometers for bubbles between [redacted] (b) (4) micrometers based on the validation batch data. The calculated osmolality for the drug product is 462 mOsm. Identity and assay test methods for glycerol and HEC were established during the review cycle and included in the release and stability specifications of the gel. The proposed shelf life of the gel is 3 years based on the stability data and is granted. The applicant agreed to provide additional elemental impurities testing for [redacted] (b) (4) and risk assessment for extractables/leachables data from the container and closure three months post-action.

[redacted] (b) (4) is the commercial manufacturer of prefilled syringes of gel and water. The firm has an acceptable Sterile Ointment (SON) profile and the facility is approvable based

on the previous history. The manufacturing process for the gel includes (b) (4) . The original submission lacked the proposed commercial packaging batch records. The applicant addressed the issue late in the review cycle and the packaging batch record is adequate to address the (b) (4) packaging of the drug-device combination.

(b) (4) . After several rounds of information requests, the applicant's response met the regulatory expectations for a sterile pharmaceutical product.

A. Special Product Quality Labeling Recommendations: None

B. Final Risk Assessment:

Drug Product (ExEm Foam)

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation
Foam concentration and size	Gel viscosity, shelf life of gel, mixing of gel and water and operator	Medium	(b) (4)	Acceptable
Identity of glycerol and hydroxyethyl cellulose	Method of manufacture, suitability of analytical methods	Medium		Acceptable
Assay of glycerol and hydroxyethyl cellulose	Method of manufacture, suitability of analytical methods	Medium		Acceptable
pH	Formulation, method of manufacture	Low		Acceptable
Impurities	.	Low		Acceptable

Microbial Limits	Components, manufacturing process.	Low	(b) (4)	Acceptable

C. Life Cycle Knowledge Information: The applicant will complete testing for (b) (4) three months post-action, and provide leachables-extractables risk assessment, as agreed in their written commitment on 10 Oct, 2019 (See applicant's response).

RBPM communication to the applicant (11/4/2019):

As agreed in your response of Oct. 10 Oct. 2019, submit test results for (b) (4) and the leachables-extractables assessment in a "Changes Being Effected" supplement, three months post-action.

Application Technical Lead Name and Date: Dhanalakshmi Kasi, Ph.D., 11/4/2019

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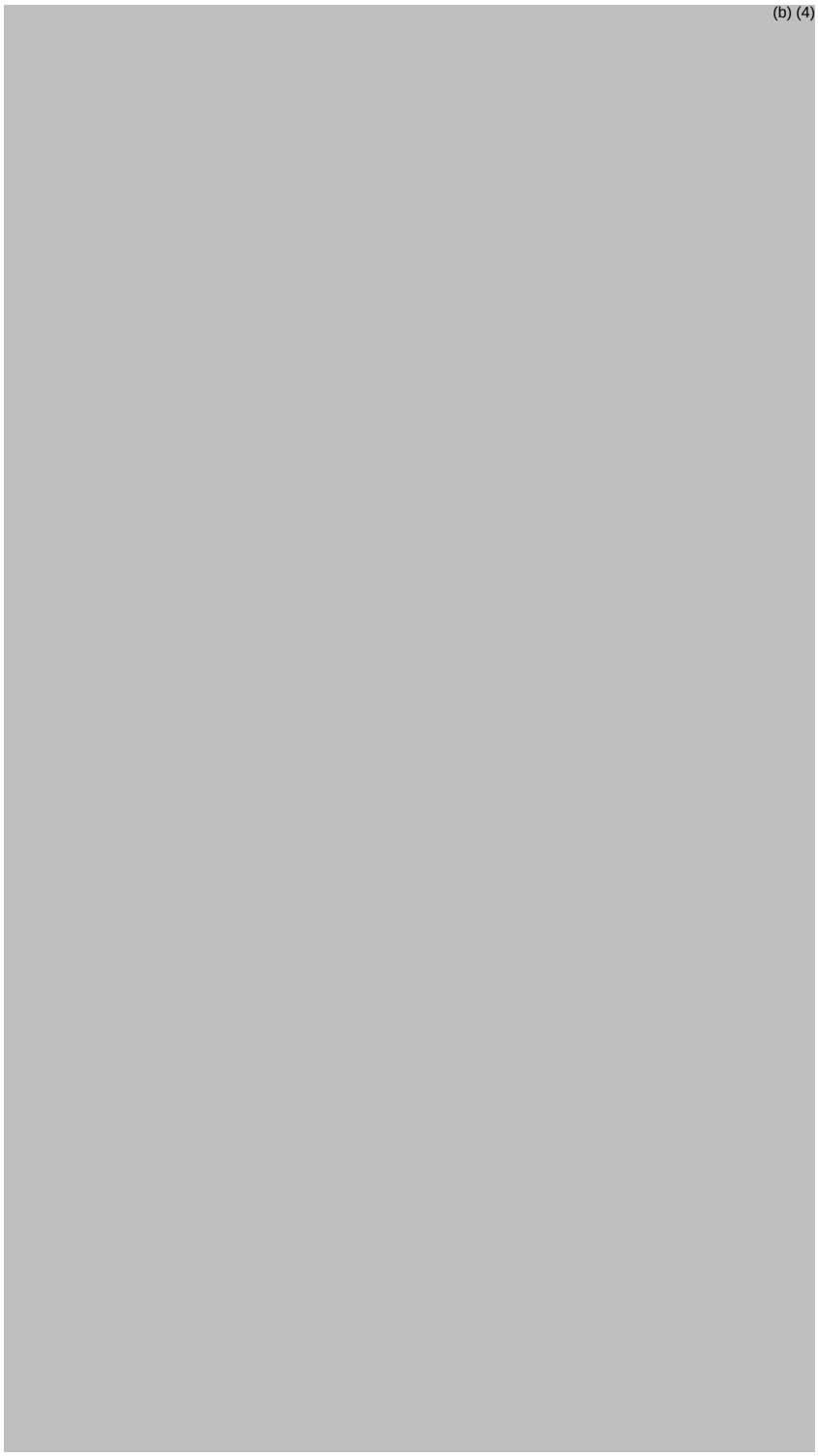
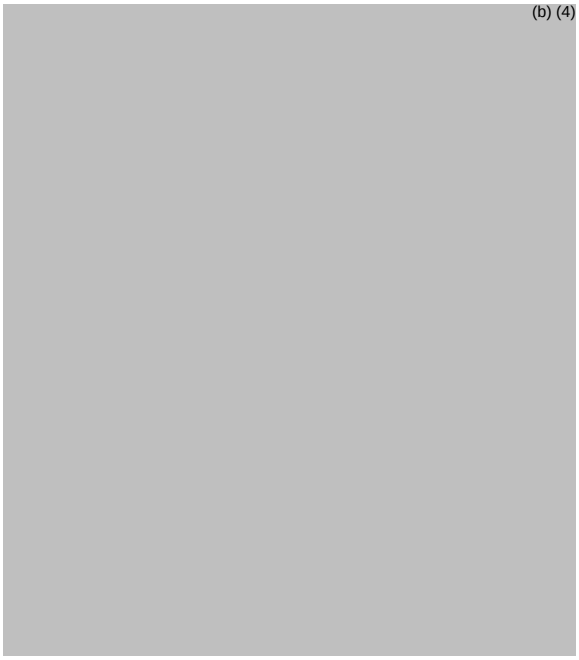
Labeling Review:

Carton

(b) (4)





Package Insert Information:

1 INDICATIONS AND USAGE:

ExEm® Foam is indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility.

2.3 Preparation and Administration

The ExEm Foam kit includes the following components:

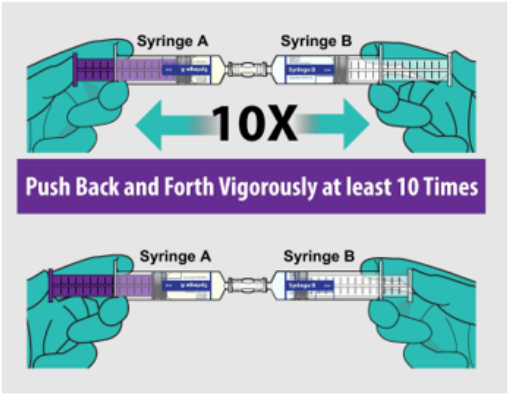
- Syringe A containing 5 mL clear Gel [polymer type A (hydoxyethyl cellulose), glycerin and purified water]
- Syringe B containing 5 mL Sterile Purified Water
- Combifix Adapter (coupling device)

Preparation

- Examine the package and **do not use if** package has been previously opened or damaged
- Ensure the kit is at room temperature
- Handle products following aseptic practices (e.g. sterile gloves)
- Generate foam by mixing Syringe A (Gel) with Syringe B (Sterile Purified Water) included in the package as described in **Figure 1.**
- Infuse foam within 5 minutes of reconstitution

FIGURE 1: Reconstitution of ExEm Foam

- Unscrew and discard the caps from each syringe when ready to prepare the foam.
- Push and screw Syringe A to one end of the Combifix Adapter.
- Push and screw Syringe B to the other end of the Combifix Adapter.
- Make sure these syringes are attached tightly to avoid loss of liquid when mixing.
- Push the plunger of one syringe vigorously to transfer, and begin mixing, the contents from one syringe to the other syringe. **Repeat this process at least 10 times.**
- The reconstituted foam is completely milky white (opaque) in color
- After mixing, transfer all of the foam into one syringe, then disconnect the adapter and other syringe.
- Approximately 10 mL of ExEm Foam is created by mixing Syringe A of clear Gel with Syringe B of Sterile Purified Water.
- **Infuse within 5 minutes of mixing** to ensure adequate imaging.



3 DOSAGE FORMS AND STRENGTHS

Intrauterine Foam, single-dose kit containing:

- Syringe A: one syringe with 5 mL clear Gel [polymer-type A (hydoxyethyl cellulose), glycerin and purified water]
- Syringe B: one syringe with 5 mL Sterile Purified Water
- One Combifix Adaptor (coupling device)

When prepared as directed ExEm Foam will contain (b) (4)

11 DESCRIPTION

ExEm Foam (air polymer-type A) intrauterine foam, is an ultrasound contrast agent. It is provided to the user for preparation as a single-dose kit containing:

* 5 mL sterile clear Gel [polymer-type A (80.97 mg hydoxyethyl cellulose), 434.80 mg glycerin 85%, and purified water]; with a pH of 6 to 7.5.

* 5 mL Sterile Purified Water; with a pH of 6 to 7.5.

After preparation, ExEm Foam is a milky-white, water-soluble intrauterine foam with an osmolality of approximately 462 mOsm and will contain between 10,000 to 127,000 bubbles per mL with a median size of 45.6 to 60.6 micrometers (for bubbles between 20 to 200 micrometers).

16 HOW SUPPLIED/STORAGE AND HANDLING

ExEm Foam is supplied as a single-dose kit, NDC 73254-310-01. Each kit contains:

- Syringe A: One sterile syringe containing 5 mL of clear Gel [polymer type A (hydoxyethyl cellulose), glycerin and purified water
- Syringe B: One sterile syringe containing 5 mL of Sterile Purified Water
- One sterile Combifix Adaptor (coupling device)

Storage and Handling

Store the kit and components at controlled room temperature between 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature]; excursions permitted at 15° to 30°C (59° to 86°F). Do not store in refrigerator. Do not freeze.

Reviewers Evaluation: The labeling team (DMIP and OPPQ), DMEPA team and drug product team discussed the content provided in the syringe, carton label and package insert provided by the applicant. Several suggestions were made and sent as information request to the applicant by the ADL, Dr. Michele Fedowitz. The applicant revised their package insert and syringe, carton label based on the suggestions provided. The updated version of the labels and package insert is provided above. Acceptable.

Dhanalakshmi Kasi

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Danae Christodoulou

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MICROBIOLOGY

Product Background:

NDA: 212279

Drug Product Name / Strength: ExEm Foam, single-use kit containing one syringe with 5 mL (b) (4) Gel, one syringe with 5 mL (b) (4) Water and a coupling device to connect the two syringes.

Route of Administration: Intrauterine infusion

Applicant Name: GISKIT B.V.

Manufacturing Site:
(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary:

List Submissions Being Reviewed: 09 October 2018 (original submission); IR responses: 14 March 2019, 15 April 2019, 23 May 2019, 07 June 2019, 03 July 2019, 24 September 2019.

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The drug product is a sterile foam indicated for the assessment of fallopian tube patency in combination with ultrasound imaging in women with known or suspected infertility (b) (4).

Concise Description Outstanding Issues Remaining: None

Supporting Documents: N/A

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Not applicable. The drug product contains no active pharmaceutical ingredient.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**

  (b) (4) gel- Almost colorless, clear, viscous liquid

  (b) (4) water- Colorless, odorless, clear liquid

- **Drug product composition –**

Ingredient	Amount in 5 mL	Function
(b) (4) **Gel**		
Glycerol 85% (EP)	434.8 (b) (4)	(b) (4)
Hydroxyethyl cellulose (HEC) (USP/NF)	80.97 (b) (4)	
Purified water (USP)	q.s.	
(b) (4) **Water**		
Purified water (USP)	5 mL	

- **Description of container closure system – (**Section 3.2.P.7, Container Closure System)

  The (b) (4) gel and (b) (4) water are filled in 11 mL syringes respectively and packaged individually in blister packs.

Configuration	Component	Description	Manufacturer
Syringe (Primary components)	Barrel (11 mL)	(b) (4)	
	Plunger		
	Tip Cap		
	Piston rod		
Blister pack (Secondary components)	Sealing of blister		
	Blister		

Adequate

Reviewer's Assessment: The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

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/s/

DHANALAKSHMI KASI
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DANAE D CHRISTODOULOU
11/06/2019 09:33:22 AM
Microbiology Chapter in OPQ Integrated Quality Assessment (IQA)signed in Panorama 9/27/2019 by Maritere Carattini and John Metcalfe. RBPM Anika Lalmansingh (OPRO) archived micro. review on 11/5/2019 in Panorama. Signatures of microbiologists will update in Panorama within 3 days of archival.