November 18, 2011

Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 51 Suckers, tubes and catheters for infusion or drainage
[Generic name]	Shunt for fetal pleural effusion
[Brand name]	Fetal Shunt
[Applicant]	Hakko Co., Ltd.
[Date of application]	November 25, 2010 (Application for marketing approval)

[Results of deliberation]
In the meeting held on November 18, 2011, the Committee on Medical Devices and *In-vitro* Diagnostics made the following decision, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product may be approved with a re-examination period of 7 years under the following conditions for approval. The product is classified as a specially controlled medical device, but is not classified as a specially designated maintenance and management-required medical device, a biological product, or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge/experience in the treatment using the product after acquiring the skills of handling the product and sufficient knowledge of possible complications associated with the procedure by attending relevant training courses or by other means.

2. Take appropriate measures to ensure that the product will be used at well-organized medical institutions staffed with physicians with a thorough knowledge of the treatment for the indicated disease who are fully capable of managing emergencies associated with the procedure using the product.

3. Register all patients treated with the product during the re-examination period, collect information on the efficacy and safety of the product from the use-results survey, and take appropriate measures as needed.

Review Report

October 31, 2011
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Classification]	Instrument & Apparatus 51 Suckers, tubes and catheters for infusion or drainage
[Generic name]	Shunt for fetal pleural effusion (to be added as a new generic name)
[Brand name]	Fetal Shunt
[Applicant]	Hakko Co., Ltd.
[Date of application]	November 25, 2010
[Reviewing office]	Office of Medical Devices II

Review Results

October 31, 2011

[Classification]	Instrument & Apparatus 51 Suckers, tubes and catheters for infusion or drainage
[Generic name]	Shunt for fetal pleural effusion (to be added as a new generic name)
[Brand name]	Fetal Shunt
[Applicant]	Hakko Co., Ltd.
[Date of application]	November 25, 2010

[Results of review]
Fetal Shunt (the product) is composed of a shunt tube that is placed in the fetal pleural cavity under ultrasonic guidance and a delivery system for the purpose of continuously draining fetal pleural effusions into the maternal amniotic cavity.

Nonclinical data on the safety, performance, stability, etc., were submitted. The data did not show any particular problems regarding clinical use. The efficacy and safety of the product in fetal pleural-amniotic shunting (fetal shunting) in patients with severe fetal pleural effusion were evaluated. Data from the foreign literature, clinical experience in Japan, and results of clinical studies conducted in Japan were submitted. These data were subjected to review on (i) whether or not the fetal shunting procedure for fetal pleural effusion is a technique already established in foreign countries (public knowledge), (ii) whether or not foreign clinical data obtained from the use of products that are different from the proposed product can be extrapolated to the Japanese population, and (iii) whether or not the safety of fetal shunting is acceptable, judging from the literature published in Japan and in other countries. In regards to the public knowledge on fetal shunting for fetal pleural effusion, it was shown in the submitted review literature that (i) fetal shunting is the most frequently used interventional treatment for severe recurrent pleural effusions as noted on fetal thoracocentesis, (ii) survival rate was 44% to 66% in fetuses receiving fetal shunting for pleural effusion associated with hydrops, and (iii) the efficacy and safety of fetal shunting have been established according to the guideline for fetal shunting in the UK. Based on the above, it was considered that fetal shunting for severe fetal pleural effusion has proven to be effective to a certain level in foreign countries. In regards to whether foreign data can be extrapolated to the Japanese population, The Japan Society of Fetal Therapy conducted a retrospective survey and a prospective clinical study was conducted under the Evaluation System of Investigational Medical Care. The results showed that the live-birth rate in Japan was equal to, or higher than, that in foreign countries, from which it has been determined that foreign data can be extrapolated to the Japanese population. In regards to treatment-related adverse events such as migration, dislocation, or dislodgement of the shunt tube, it was considered necessary to provide appropriate information via the package insert, to obtain informed consent upon providing thorough information, and to perform the treatment under a well-controlled system staffed with specialists capable of reducing the treatment-associated risks and taking appropriate measures promptly in the case of adverse events.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following intended use, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
Fetal Shunt is used to continuously drain pleural effusion from the fetal pleural cavity into the amniotic cavity when thoracocentesis is not effective.

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge/experience in the treatment using the product after acquiring the skills of handling the product and sufficient knowledge on possible complications associated with the procedure by attending relevant training courses or by other means.

2. Take appropriate measures to ensure that the product will be used at well-organized medical institutions staffed with physicians with a thorough knowledge of the treatment for the indicated disease who are fully capable of managing emergencies associated with the use of the product.

3. Register all patients treated with the product during the re-examination period, collect information on the efficacy and safety of the product from the use-results survey, and take appropriate measures as needed.

Review Report

October 31, 2011

I. Product for Review

[Classification]	Instrument & Apparatus 51 Suckers, tubes and catheters for infusion or drainage
[Generic name]	Shunt for fetal pleural effusion (to be added as a new generic name)
[Brand name]	Fetal Shunt
[Applicant]	Hakko Co., Ltd.
[Date of application]	November 25, 2010
[Proposed intended use]	Fetal Shunt is used to continuously drain the pleural effusion from the fetal pleural cavity into the amniotic cavity by inserting a shunt tube through the fetal chest wall to place the shunt tube between the fetal pleural cavity and the maternal amniotic cavity, thereby improving fetal hydrops, preventing pulmonary hypoplasia, and prolonging the gestational period.
[Items warranting special mention]	Orphan medical device

II. Product Overview

The product is a fetal shunt system comprising a shunt tube that is placed to continuously drain the fetal pleural effusion into the maternal amniotic cavity and a delivery system to deliver the shunt tube to the intended site of shunt tube placement. Both ends of the shunt tube (1.5 mm ϕ at the site of placement, 50-70 mm in length) have a basket shape (Figure 1) that is appropriate for placement between the fetal pleural cavity and maternal amniotic cavity. The shunt tube is inserted percutaneously into the uterus using a delivery system (1.5 mm ϕ) under ultrasonic guidance. A marketing application for the product has been filed by Hakko Co., Ltd.; the intended use is for improving fetal hydrops, preventing pulmonary hypoplasia, and prolonging the gestational period of fetuses with pleural effusion.

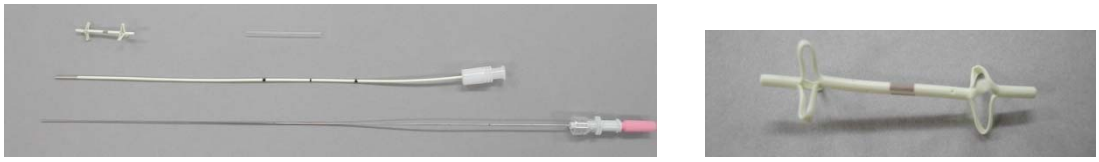

Figure 1. Shunt tube and delivery system (left), enlarged image of the shunt tube (right)

III. Summary of the Submitted Data and the Outline of the Review by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors of the Expert Discussion on this product declared that they do not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. Origin or history of discovery and usage conditions in foreign countries etc.

[Origin or history of discovery]

Fetal pleural effusion is an abnormal build-up of fluid within the pleural cavity of fetuses. Fetal pleural effusions are roughly classified into primary and secondary fetal effusions. Primary fetal pleural effusion, which is not associated with other abnormalities, occurs in 1 out of 10,000 to 15,000 pregnant women,[1)2)] and is usually caused by congenital chylothorax. Secondary fetal pleural effusion occurs as a part of other diseases, and known primary diseases include cardiac disease, hematologic disease, infection, chromosomal aberration, and cystic lung disease. Primary fetal pleural effusion sometimes resolves spontaneously. Aubard et al. reported that 22% of patients had pleural effusion that resolved spontaneously.[3)] In some patients, on the other hand, fluid accumulation within the pleural cavity leads to pulmonary hypoplasia, heart compression, and obstruction of the venous blood circulation, sometimes leading to serious conditions such as hydrops and polyhydramnios. The natural history of primary fetal pleural effusion varies in the literature, but the overall perinatal mortality rate is reported to be 22% to 53%.[4)] In contrast, the perinatal mortality rate of fetuses with hydrops, among those with pleural effusion, was reported to be 52%[2)] or 75%[5)], suggesting the seriousness of fetal pleural effusion associated with hydrops.

Conventional therapies for fetal pleural effusion include thoracocentesis (TC). Since TC is performed using a very fine centesis needle, each centesis is minimally invasive. After Petre et al. successfully attempted to remove fetal pleural effusion by suction from the maternal body surface using a centesis needle under ultrasonic guidance in 1982, TC has been performed as the standard treatment for fetal pleural effusion. For cases where body fluid accumulation recurs within a short time after TC, fetal pleural-amniotic shunting (fetal shunting) is indicated, which was reported by Seeds et al. in 1986, in order to avoid the risk of membrane rupture or threatened premature delivery caused by stimuli and/or infection caused by multiple centesis procedures in TC. Thereafter, the usefulness of fetal shunting has been reported extensively in the literature. In Japan, the National Cardiovascular Center was accredited in 2005 as a qualified institution to perform fetal shunting as a highly advanced medical treatment, which was followed by the accreditation of four other institutions. From April 2008, the proposed product was subjected to evaluation under the Evaluation System of Investigational Medical Care (Fetal pleural-amniotic shunting is one of the advanced medical treatments specified in MHLW Ministerial Announcement No. 129-3 of 2008) and a clinical study was conducted in Japan from 2008 through 2010.

The product was designated as an orphan medical device on March 19, 2010 (PFSB/ELD/OMDE Notification No. 0319-1 dated March 19, 2010).

[Usage conditions in foreign countries]

The product has not been approved or used in clinical practice in any foreign country. As described in the "Origin or history of discovery" section, there are similar products used for fetal shunting for fetal pleural effusion, including Rocket double pigtail silastic catheter (Rocket Medical), Harrison shunt (COOK Medical), and Angiographic single pigtail catheter (Johnson & Johnson), all of which are pig tail-shaped catheters and are not approved for the indication of fetal pleural-amniotic shunting, and are different from the proposed product in shape, materials, etc.

2. Setting of specifications

The specifications for the product include extensibility and appearance of the shunt tube; tensile strength, appearance, and operability of the delivery system; extractable substances and biological safety of the shunt tube and the delivery system; appearance, bending strength, tensile strength, extractable substances, biological safety, and operability of the introducer needle; and sterility of and residual ethylene dioxide in the product as a whole.

PMDA considered that the shunt tube should maintain mechanical strength after being placed in the fetus because (i) it has to be patent to maintain continuous drainage and (ii) it is used in a fetus that moves actively. PMDA also considered that the stylet needle should also have sufficient mechanical strength for guiding the shunt tube to the fetal pleural cavity. Based on the above, PMDA asked the applicant to reconsider the product specifications.

The applicant replied as follows:
To ensure the patency of the shunt tube, extensibility and collapse are included in the specifications. The testing method for extensibility proposed initially in the application was visual confirmation of "the extensibility of the open end." However, in order to make the specification more quantitative, the testing method was revised to measure the length of the basket at extension and confirm that the observed value is the same as that described in the application. In regards to collapse, it will be confirmed that the lumen of the shunt tube does not collapse when a load of 1 N is applied. When the contact area is taken into account, the load of 1 N corresponds to [redacted] mmHg. Given that the intrapleural pressure in typical patients with pleural effusion is 39 mmHg and that the pressure in the amniotic cavity is 21 mmHg, the above pressure is higher than these values. Therefore, the patency of the product in the ambient pressure will be sufficiently maintained. In order to ensure that the mechanical strength of the shunt tube is sufficient, the specifications will include tensile strength and it will be confirmed that the tube does not break down when a load of 15 N is applied. The load was selected to be approximately 3 times that described for the stent and drainage catheter for the biliopancreatic duct, taking account of the facts that the tensile strength specified in JIS T 3269 "Stent and drainage catheter for biliary and pancreatic ducts" is 4.9 N, and that the tensile strength specified in JIS T 3270 "Ureteral tube stent for long-term use" is 3.9 N. These devices are used under severer conditions compared with the proposed product, judging from the environment of placement, duration of placement, and conditions for clinical use. Therefore, a tensile strength three times greater than those of the above-mentioned devices is considered sufficient for the product. In order to ensure the mechanical strength of the stylet of the delivery system, bending strength was included in the specifications and the testing method was in accordance with JIS T 3209 "Sterile injection needles." Since the shunt tube and the delivery system are made of the same materials and have the same diameter, they will be subjected to the common kink test; the specifications will follow those described in JIS C 6851 "Optical fiber cable test procedures." In clinical studies of the product that conformed to the above specifications, there were no serious adverse events related to any of the above test items; therefore, the applicant determined that the above specifications were appropriate as a whole.

As a result of reviewing the specifications, including "Performance" to be described later, for the appropriateness of the attributes tested and the specification limits, PMDA accepted the proposed specifications.

3. Stability and durability

A written statement was submitted, declaring that the materials, manufacturing process, and sterilizing method of the shunt tube and the delivery system are the same as those of an approved product of the applicant "Internalized catheter set" (20100BZZ01274000), and those of the introducer needle are the same as those of an approved product of the applicant "Elaster injection puncture needle" (16300BZZ01584000). The tube of the Internalized catheter set is a device

intended for biliary drainage, and is used under severer conditions than the proposed product, judging from the environment of placement, duration of placement, and conditions for clinical use. The introducer needle is identical to the needle of the proposed product and, in the proposed product, it is used without deviation from the original intended use. Therefore, PMDA accepted the explanation of the applicant that the stability of the proposed product is assured without the need for any additional testing.

The shunt tubes before and after use were subjected to tests that assessed the appearance, breaking strength, and deterioration. Results showed that both ends remained open, the breaking strength remained unchanged, and Fourier transform infrared spectroscopy (FTIR) did not detect any deterioration of the tube. These results were submitted as reference data.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

A declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (MHLW Ministerial Announcement No.122, dated March 29, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169, dated December 17, 2004) was submitted.

5. Performance

[Studies supporting safety]

The applicant explained that the shunt tube and the delivery system are manufactured using the same materials, manufacturing process, and sterilizing method as those used for the above approved products of the applicant and therefore, their biological safety is assured without the need for further tests, judging from the use conditions. PMDA accepted the explanation of the applicant.

[Tests supporting performance]

The following tests were conducted to assess performance.

(1) Shunt tube

It was confirmed that the shunt tube met the acceptance criteria for test parameters included in the specifications.

Regarding the extensibility test, taking account of the fact that the proposed product is placed within the amniotic cavity, PMDA asked the applicant whether or not the internal pressure of the amniotic cavity had been taken into account in the test. PMDA also asked the applicant whether or not visually confirming the extensibility of the open end was appropriate because the acceptance criteria were based on subjective judgment.

The applicant provided the following explanation:

This test checks whether or not the shape remains unchanged for ■ minutes at 37°C in physiological saline. In addition to this test, the shunt tube was subjected to hydraulic pressure of 530 mmH_2O corresponding to 39 mmHg (assuming the inner pressure of the pleural cavity and amniotic cavity in actual use are 39 and 21 mmHg, respectively). Results showed that the shunt tube extended without being affected by the external pressure. The acceptance criteria were changed to a quantitative one where the height of the both baskets (the outermost length of each basket in the longitudinal direction of the shunt tube) at extension is measured to confirm that the height conforms to that described in the application.

(2) Other specifications

With respect to other performance data on the product, data showing that the product conformed to the acceptance criteria were submitted.

[Studies supporting efficacy]
With respect to evidence that supports the efficacy of the proposed product, the patency of the product after placement was demonstrated by the results of the extensibility study in [Tests supporting performance] in "5. Performance." It was also explained that the maintenance of patency was confirmed by observing the appearance of the recovered product after usage, suggesting that the sufficient drainage effect would be expected.

[Studies supporting usage method]
To support the usage of the proposed product, data of Visual confirmation of shunt tube with a roughened surface were submitted. The central part of the tube of the product has a rough surface that is visible on ultrasound scanning. It was confirmed that the roughened surface was visible on ultrasonography when the product is immersed in water at 37°C.

[Clinical evaluation]
With regard to data on the clinical evaluation of the product, literature on fetal shunting for the treatment of fetal pleural effusion in foreign countries and literature on clinical study results in Japan were submitted. A literature search was performed according to the following procedures. Literature in the database MEDLINE was searched using the keywords "fetal pleural effusion" and "shunt" and a total of 360 documents were retrieved. By excluding public guidelines and duplicate studies in the Japanese literature that were extracted by subsequent searches using JMEDPlus, 14 documents were identified that reported malfunctions in fetal shunting (Table 1). In a similar manner, 130 documents were retrieved by searching JMEDPlus with the keywords "fetal hydrops," "amniotic cavity shunts," and "fetal pleural cavity centesis." From the retrieved literature, those that met all of the following criteria were selected: (i) those published in or after 2000, (ii) those that reported cases of fetal shunting, and (iii) those that reported malfunctions. A total of 15 documents met these criteria and were subjected to clinical evaluation (Table 2).

Table 1. List of the 14 documents in the foreign literature that were evaluated

No.	Abstract/title/authors/source
1	Report on the perinatal outcome of fetal pleural effusion treated with shunting Perinatal outcome following fetal chest shunt insertion for pleural effusions. Yoav Yinon MD, Sorina Grisaru-Granovsky MD, Vandana Chaddha MD, Rory Windrim MB, P Gareth R. Seaward MB, Edmond N. Kelly MB, Olena Beresovska MD, Greg Ryan MB *Ultrasound Obstet Gynecol*. 2009;Dec 9
2	Explanation of the usefulness of, and approach for, shunting for fetal pleural effusion Fetal pleural effusions. Yoav Yinon MD, Edmond Kelly MD, Greg Ryan MD *Best Pract Res Clin Obster Gynaecol*. 2008;Vol.22,No.1,pp77-96
3	Efficacy of interventional treatments of fetal pleural effusion (therapies: thoracocentesis, shunting, pleurodesis) Fetal pleural effusion. Maria Angela Rustico, Maroano Lanna, Dario Coviello, John Smoleniec and Umberto Nicolini *Prenat Diagn*. 2007;27:793-799
4	Report of perinatal outcome of fetal pleural effusion complicated with hydrops caused by prenatal treatment Isolated fetal hydrothorax with hydrops: a systematic review of prenatal treatment options. K.L.Deurloo, R.Devlieger, E.Lopriore, F.J.Klumper, D.Oepkes *Prenat Diagn*. 2007;27:893-899
5	Report of shunting fetal pleural effusion in twin pregnancy Intrathoracic Pressure in Congenital Chylothorax: Keystone for the Rationale of Thoracoamniotic shunting? Masami Yamamoto, Alvaro Insunza, Jorge Carrillo, Luis Alberto Caicedo, Enrique Paiva, Yves ville *Fetal Diagnosis Therapy*. 2007;22:169-171

No.	Abstract/title/authors/source
6	NHS report on interventional treatment pertaining to shunting Interventional procedure overview of insertion of pleural-amniotic shunt for fetal pleural effusion. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE NHS March 2006
7	NHS guideline for shunting Insertion of pleuro-amniotic shunt for fetal pleural effusion. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE Interventional procedure guidance 190, September 2006
8	Report of long-term follow-up evaluation of 3 cases of fetal pleural effusion treated with shunting Intrathoracic dislodgement of pleuro-amniotic shunt. Three case reports with long-term follow-up. Waldo Sepulveda, Alberto Galindo, Alberto Sosa, Luis Diaz, Ximena Flores, Pedro de la Fuente *Fetal Diagn Ther*. 2005;20:102-105
9	Report on the outcome of patients with pleural effusion or with cystic form, congenital cystic adenomatoid malformation who received shunting or those who did not Thoracoamniotic Shunts: Fetal Treatment of Pleural Effusions and Congenital Cystic Adenomatoid Malformations. R.Douglas Wilson, Jason K. Baxter, Mark P. Johnson, Mary King, Stefanie Kasperski, Timothy M. Crombleholme, Alan W. Flake, Holly L.Hedrick, Lori J. Howell, N. Scott Adzick *Fetal Diagn Ther*. 2004;19:413-420
10	Report on the perinatal outcome of shunting for fetal pleural effusion with hydrops Thoracoamniotic Shunting for fetal pleural effusions with hydrops. Olivier Picone MD, Alexandra Benachi MD PhD, Laurent Mandelbrot MD, Rodrigo Ruano MD, Yves Dumez MD, Marc Dommergues MD *American Journal of Obstetrics and Gynecology*. 2004;191:2047-2050
11	Report on the outcome of shunting for patients with pulmonary sequestration Fetal thoracoamniotic shunting as the only treatment for pulmonary sequestration with hydrops: favorable long-term outcome without postnatal surgery. L. J.SALOMON, F.AUDIBERT, M.DOMMERGUES, M.VIAL, R.FRYDMAN *Ultrasound Obstet Gynecol*. 2003;21:299-301
12	Proposal of a strategy for clinical treatment of prenatally detected fetal pleural effusion based on the review of 64 literature documents Primary Fetal Hydrothorax: A Literature Review and Proposed Antenatal Clinical Strategy. Aubard Y, Derouineau I, Aubard V, Chalifour V, Preux PM *Fetal Diagn Ther*. 1998Nov-Dec;13(6):325-33
13	Report of the outcome of natural history and management of fetal pleural effusion Primary Fetal Hydrothorax: Natural History and Management. Longaker MT, Laberge JM, Dansereau J, Langer JC, Crombleholme TM, Callen PW, Golbus MS, Harrison MR *Journal of pediatric surgery*. 1989 Jun;24(6):573-576.
14	Report on the outcome of bilateral fetal pleural effusion treated with shunting Case Reports: Results of Treatment of Severe Fetal Hydrothorax with Bilateral Pleuroamniotic Catheters. John W.Seed MD, Watoson A.Bowes,jr MD *Obstetrics&Gynecology*. Vol. 68,No.4,October 1986

Table 2. List of 15 documents in the Japanese literature that were evaluated

No.	Abstract/title/authors/source
15	Report on the efficacy and safety of thoracocentesis and shunting for fetal pleural effusion Study on the treatment of fetuses with fetal pleural effusion Miura Y, Sago H, Takahashi H, Hayashi S, Nakamura K, Ito Y, Kubo T, Kitagawa M *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2009;45(4):1311-1316
16	Explanation of treatment methods and efficacy for fetal blood transfusion, fetal pleural effusion, fetal tachyarrhythmia, acardiac twin, and lower urinary tract obstruction Perinatal management and fetal treatment evaluated by outcome Sago H, Hayashi S, Aoki H *Journal of Japan Society of Perinatology.* 2009;39(10):1381-1385

No.	Abstract/title/authors/source
17	Case report of shunting for extralobar pulmonary sequestration that resulted in catheter dislodgement A case of prenatally diagnosed extralobar pulmonary sequestration who underwent operation during the neonatal period Kato T, Hibi M, Okumura N, Tomishige H, Hara F, Hashimoto S *Journal of the Japanese Society of Pediatric Surgery*. 2009;45(2):249
18	Explanation of shunting and report of the clinical results at National Hospital Organization Nagara Medical Center Clinical conference 6: Recent progress in fetal treatment, 1) Treatment of fetal pleural effusion by intrauterine shunting Takahashi Y *The Journal of Obstetrics and Gynaecology Research*. 2008; 60(9):278-281
19	Case reports of fetal pleural effusion treated with thoracocentesis or shunting at Maternal and Perinatal Care Center, Seirei Hamamatsu General Hospital Clinical studies on 12 cases of fetal pleural effusion Ueda T, Murakoshi T, Numada M, Tsubokura K, Matsumoto M, Adachi H, Shibuya S, Naruse H, Torii Y, Ueda M *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2007;43(4):1043-1047
20	Report on the efficacy of shunting for pulmonary sequestration Up-to-date information on fetal surgery: Pleural effusion-amniotic cavity shunting for fetal pleural effusion caused by pulmonary sequestration Kubota A, Okuyama H, Takahashi T, Ikegami R, Kawahara H, Nakai H, Yoshida H, Takama Y, Suehara N *Journal of the Japanese Society of Pediatric Surgery*. 2005;37(6):674-679
21	Case report of shunting for a fetus who developed pneumothorax after birth A case of primary fetal pleural effusion with residual free air after birth caused by insufficiency in pleural cavity-amniotic cavity shunt Kuratsuji G, Hokuto I, Hida M, Ikeda K, Matsumoto T, Tanaka M *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2005;41(2):231
22	Overview of the fetal treatment history and shunting in Japan Fetal diagnosis and treatment Chiba Y *Japanese Journal of Pediatric Urology*. 2004;13(2):107-111
23	Case report of fetal pleural effusion treated with shunting at Kanagawa Children's Medical Center A case of fetal left chylous pleural effusion treated *in utero* with pleural–amniotic shunting Hashimoto S, Setoyama T, Hirabuki T, Toyoshima K, Kawataki M, Igaya Y, Yamanaka M *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2004;40(1):81-85
24	Case report of fetal pleural effusion treated with shunting at Kanagawa Children's Medical Center Complication associated with fetal pleural cavity-amniotic cavity shunting in a patient with fetal pleural effusion Yamanaka M, Hirabuki T, Hashimoto S, Setoyama T, Aoyama M, Igaya Y *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2003;39(2):347
25	Case report of amniotic fluid reflux from the amniotic cavity to the pleural cavity through the shunt tube A case of fetus with fetal chylothorax who showed reflux of amniotic fluid into pleural cavity through an inserted basket catheter Shimada K, Suzuki N, Kameyama Y, Sugawara J, Okamura K *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2003;39(2):347
26	Case report of shunting in bilateral fetal pleural effusion A case of bilateral fetal pleural effusion treated *in utero* with a double-basket catheter Suzuki D, Shiozaki A, Sakai M, Tabata M, Sasaki Y, Yoneda T, Yoshida T, Nitani T, Saito S *Journal of Japan Society of Perinatal and Neonatal Medicine*. 2003;39(2):346
27	Overview of current status of fetal treatment in Japan Future trend of fetal care: Current and future status of fetal treatment Chiba Y *Obstetrical and Gynecological Therapy*. 2002;84(1):1-9
28	Report of a method for pleurodesis using OK-432 A case of successful fetal therapy for congenital chylothorax by intrapleural injection of OK-432 Tanemura M, Nishikawa N, Kojima K, Suzuki Y, Suzumori K *Ultrasound Obstet Gynecol*. 2001 Oct;18(4):371-375

No.	Abstract/title/authors/source
29	Report of a method for pleurodesis using OK-432 A new fetal therapy for chylothorax: pleurodesis with OK-432 Okawa T, Takano Y, Fujimori K, Yanagida K, Sato A *Ultrasound Obstet Gynecol* 2001 Oct;18(4):376-377

Of the submitted data, literature 4 and 12 are systematic reviews, and literature 2 and 3 are reviews (reviews based on non-systematic literature search). Literature 7 is a guideline for fetal pleural shunting published by the UK National Institute for Health and Clinical Excellence (NICE) of the National Health Service (NHS), and literature 6 is a summary of the treatment method. The outlines of the literature are described below. The results of clinical studies in Japan are also summarized. Other literature include results of clinical studies and case reports; these results were not inconsistent with the following description. Safety was evaluated based on the adverse events reported in the submitted data.

[Outline of the literature from foreign countries]
Literature 4
Literature published during the period from January 1982 through January 2006 was subjected to a systematic review to evaluate the effect of prenatal treatment on the perinatal outcome in pregnancies complicated by isolated fetal pleural effusion with hydrops. Results of review of 44 reports that met the inclusion criteria showed that the treatment method used was TC (once, n = 13; multiple, n = 18), fetal shunting (n = 100), and combination of TC and fetal shunting (n = 36), with fetal shunting being the most frequently used method. The survival rate was 67% for TC and 61% for fetal shunting alone. Risks associated with fetal shunting included failure of placement, re-intervention, dislocation or migration of shunt and, in rare cases, contracture of extremities or umbilical cord. No data from randomized studies or controlled studies were retrieved by the literature search, which is unavoidable because of the low survival rate in watchful waiting, and given the possible publication bias, collecting reliable outcome data was considered possible to a limited extent. Thus, the review report points out that although caution is required in interpreting the observed survival rate, prenatal treatment of fetuses with isolated pleural effusion with hydrops is beneficial to some extent, and recommends that invasive fetal treatment such as fetal shunting be performed at experienced specialized medical institutions.

Literature 12
This is a systematic review of reports on primary fetal pleural effusion published in French or in English during the period from 1977 through 1996. The review was done to investigate the prognostic factors of primary fetal pleural effusion and to propose a clinical strategy. Based on 64 reports that met the inclusion criteria, an evaluation of prognostic factors and intrauterine treatment (e.g., TC, fetal shunting, pleural percutaneous drainage) was made. The prognostic factors described in untreated patients, including the presence or absence of hydrops, and treatments used are listed below. It was reported that the highest fetal survival rate was obtained by fetal shunting if it had been performed before 32 weeks of pregnancy in fetuses with advanced pleural effusion with poor prognostic factors (such as presence of hydrops), but the management method differs depending on the gestation period. Reported malfunctions include catheter dislocation, catheter occlusion, shunt backflow, and ascitic fluid in the maternal body after placement.

Table 3. (Literature 12) Prognostic factors of untreated primary fetal hydrothorax (PFHT)

	Perinatal death	Survival of neonate	*P*
Mean gestational age at diagnosis (weeks)	28.25 (4.79)	27.02 (7.63)	NS
With hydrops (%)	76	24	
Without hydrops (%)	25	75	<0.001
Spontaneous remission	0	100	
No spontaneous remission	51	49	<0.001
Bilateral	47	53	
Unilateral	23	77	<0.05
Mean gestational age at delivery (weeks)	31.97 (4.04)	34.78 (2.56)	<0.001

Table 4. (Literature 12) Outcome of fetuses as a function of presence/absence of hydrops and treatment method used

	Survival after thoracocentesis	Survival after shunting	Survival without treatment	*P*
With hydrops (%)	10 (19)	66.6 (63)	23.5 (17)	<0.01
Without hydrops (%)	60 (10)	100 (17)	21.3 (48)	<0.05

*The number in the parentheses indicates the number of patients.

Literature 2

This is an overview of the treatment of primary fetal pleural effusion. The review concludes that bilateral pleural effusion, hydrops, premature birth, and lack of prenatal treatment result in a poor prognosis, and that, if structural anomaly and chromosomal aberration are excluded, the optimal treatment depends on the gestational age, extent of progression, occurrence of hydrops, and related symptoms of the maternal body. Interventional treatment of fetuses is justified for massive pleural effusion with a mediastinal shift, hydrops and/or polyhydramnios, and for cases with a rapidly increasing pleural effusion. The perinatal survival rate with fetal shunting is 60% to 100% in cases without hydrops and 44% to 66% in cases with hydrops (see Table 5). According to the report of Rustico et al. on 53 fetuses who underwent fetal shunting, clinical abnormalities were observed in 10 infants in the follow-up study (for 1 to 7 years), while 24 infants survived without any abnormality.

Table 5. (Literature 2) Results of fetal shunting in single large-scale institutions

Institution location	Year	Number of subjects		Gestational age at shunting (median)	Gestational age at delivery (median)	Remission of hydrops	Perinatal survival rate	
		With hydrops	Without hydrops				With hydrops	Without hydrops
London (1)	1997	41 (59%)	28 (41%)	29	36	19 (46%)	19 (46%)	28 (100%)
Paris (2)	2004	47	0	30.5	34		31 (66%)	
Bristol (3)	2005	16 (76%)	5 (24%)	24	32		7 (44%)	3 (60%)
Milan (4)	2007	43 (81%)	10 (19%)	NA	NA	NA	25 (58%)	9 (90%)

[1] Pattersen HN & Nicolaides KH. Pleural effusions. In Fisk NM & Moise KJ(eds.). Cambridge: *Cambridge University Press*. 1997, pp. 261-272

[2] Picone O, Benachi A, Mandelbrot L et al. Thoracoamniotic shunting for fetal pleural effusions with hydrops. *Am J Obset Gynecol.* 2004;191:2047-2050

[3] Smith RP, Illanes S, Denbow ML et al. Outcome of fetal pleural effusions treated by thoracoamniotic shunting. *Ultrasound Obset Gynecol.* 2005;26:63-66

[4] Rustico MA, Lannna M, Coviello D et al. Fetal pleural effusion. *Prenat Diagn*. 2007 Jun 29

Literature 3

This review evaluated the improvement of the survival rate after intrauterine intervention (repeated TC, fetal shunting, pleurodesis) for fetuses with persistent pleural effusion. The survival rate of fetuses with primary pleural effusion with hydrops was 35% if intrauterine treatment had not been given and 62% if intrauterine treatment had been given (see Table 6). The best outcome

was obtained by fetal shunting regardless of presence or absence of hydrops. The review concluded that fetal shunting improves the outcome, particularly in fetuses with hydrops and those who are likely to develop hydrops, based on accumulated literature information, although no randomized study on the operation has been conducted.

Table 6. (Literature 3) Outcome of 203 fetuses (reported in the literature) with suspected primary pleural effusion that underwent different treatments (number and percentage of subjects) and gestational age at the first observation (mean, range)

	With hydrops	Without hydrops	Total
Thoracocentesis	n = 22	n = 13	n = 35
Gestational age at treatment (weeks)	-	-	29 (17-36)
Abortion	3 (14%)	-	3 (9%)
Intrauterine death	1 (4%)	-	1 (3%)
Neonatal death	7 (32%)	3 (23%)	10 (28%)
Survival	11 (50%)	10 (77%)	21 (60%)
Pleural cavity-amniotic cavity shunting	n = 125	n = 33	n = 158
Gestational age at treatment (weeks)	-	-	26 (16-35)
Abortion	4 (3%)	3 (9%)	7 (4%)
Intrauterine death	20 (16%)	-	20 (13%)
Neonatal death	24 (19%)	3 (9%)	27 (17%)
Survival	77 (62%)	27 (82%)	104 (66%)
Pleurodesis	n = 6	n = 4	n = 10
Gestational age at treatment (weeks)	-	-	25 (14-31)
Abortion	-	-	-
Intrauterine death	2	-	2 (20%)
Neonatal death	1	1	2 (20%)
Survival	3	3	6 (60%)

Literature 6 and 7
These reports (6 and 7) relate to the program of the NHS of the UK on interventional treatment (outline of interventional treatment pertaining to pleural-amniotic shunting for fetal pleural effusion) and its guidance, respectively.

The guidance issued in 2006 states that "the safety and efficacy of pleural-amniotic shunting for draining fetal pleural effusion have been established, while there are uncertainties about the natural course of fetal pleural effusion and about patient selection." Therefore, the guideline requires that informed consent should be obtained after providing written information to family members to help them understand the uncertainties about the natural course and patient selection, and that treatment should be given at a specialized institution staffed with physicians who specialize in fetal treatment and with many expert teams. Also, the NHS interventional procedures program (Interventional procedure overview of insertion of pleural-amniotic shunt for fetal pleural effusion) states that currently available treatment options for prenatal intervention include thoracocentesis and pleural fluid drainage that allow normal pulmonary development and prevent hydrops, and that the initial treatment should be needle aspiration drainage and if re-accumulation is observed by a repeated scan, shunt insertion should be considered.

[Use results in Japan and clinical studies under the Evaluation System of Investigational Medical Care]
Data on fetal shunting using the proposed product in Japan were obtained from a report published by the Japan Society of Fetal Therapy on the retrospective survey of fetal shunting from 2002 through 2006. There were only 7 institutions that performed fetal shunting for ≥5 fetuses during the above period. Data were accumulated from a total of 71 subjects, 42 of whom survived, with a survival rate of 59%.

Data from a clinical study that was conducted under the Evaluation System of Investigational Medical Care and published on the homepage of the Japan Fetal Therapy Group at the National Center for Child Health and Development were also provided. This clinical study was conducted from 2008 through 2010 as a multi-center, single-arm study using the survival rate of children at 28 days after birth as the primary endpoint. Mothers included in the study were those with a single pregnancy from Day 0 in Week 18 to Day 6 in Week 33 of gestation with a fetus who developed unilateral or bilateral massive pleural effusions and had re-accumulation within 7 days after TC (regardless of the presence or absence of fetal hydrops). Subjects with any of the following prognostic factors were excluded: morphological anomaly, fetal arrhythmia, intracranial calcification, fetal anemia, serious chromosomal aberration, a mother with a negative indirect Coombs test, mirror syndrome, pregnancy-induced hypertension, and signs of threatened premature delivery (cervical dilation ≤10 mm, membrane rupture). Data were accumulated from 24 fetuses over 2 years, and fetal shunting was performed using the proposed product in 23 fetuses except for one fetus whose mother refused treatment. Table 7 summarizes the results.

Table 7. Summary of the clinical study conducted under the Evaluation System of Investigational Medical Care

Perinatal information			Summary of adverse events	
Preoperative background			On the day of shunting	
Treatment period	27 weeks and 3 days (20 weeks and 6 days-32 weeks and 6 days)		Pain	Mild (12), moderate (1)
			Haemorrhage foetal	Mild (2)
Estimated baby weight	1311 g (383-2348)		Haemorrhage of maternal body	Mild (6)
			Bradycardia foetal	0
Survival rate at 28 days after birth			Rupture of membranes	0
With hydrops	12/17 (70.6%)		Management of threatened premature labour	17/24 (71%)
Without hydrops	7/7 (100%)			
Total	19/24 (79.2%)			
			Up to delivery	
Mean body weight at birth (SD)	2272g (553.7)		Polyhydramnios after shunting	6/11 (54.8%)
			Intrauterine infection	0/22 (0%)
Change in skin edema after shunting (before birth)		Neonatal death*	Pregnancy-induced hypertension	1/22 (4.5%)
Complete remission	7 (43.8%)	0		
Partial remission	4 (25%)	1	Placental abruption	0/22 (0%)
No change	2 (12.5%)	0	Foetal dysfunction	0/22 (0%)
Progression	3 (18.8%)	3	Catheter dislodgement	4/42 treated (9.5%)
	*Excluding drop-out cases		mirror syndrome	3/24 (13%)
			Premature rupture of membranes (within 7 days after shunting)	0/24 (0%)
			Premature rupture of membranes (within 28 days after shunting)	1/24 (4.2%)

The survival rate of newborns at 28 days after birth was 79.2% (19 of 24 fetuses). The survival rate was 70.6% (12 of 17 fetuses) in those with fetal hydrops before treatment and 100% (7 of 7 fetuses) in those without fetal hydrops. Of those with fetal hydrops, 11 fetuses (69%) showed an improvement in hydrops (complete disappearance of subcutaneous edema in 7 fetuses, improvement of subcutaneous edema in 4 fetuses), whereas 3 fetuses worsened. The median treatment duration was 27 weeks and 3 days, and the median duration before birth was 34.8 weeks. Adverse events that were observed from Day 7 to Day 28 were premature rupture of membranes in 1 mother and catheter dislodgement into the fetal pleural cavity in 4 fetuses, none of which were serious or resulted in death.

Adverse events observed on the day of the operation were mild pain (12 of 24 mothers), threatened premature delivery (17 of 24 mothers), moderate pain (1 of 24 mothers), foetal haemorrhage (2 of 24 fetuses), and maternal haemorrhage (6 of 24 mothers). Adverse events that were observed in the interval from the day of the operation up to delivery were premature rupture of membranes (1 of 24 mothers), polyhydramnios (6 of 11 mothers), pregnancy-induced hypertension (1 of 22 mothers), and mirror syndrome (3 of 24 mothers/fetuses). Catheter dislodgement occurred in 4

out of 42 operations. The following adverse events had been expected but were not observed in this study: intrauterine infection, placental abruption, foetal dysfunction, foetal bradycardia on the day of operation, and membrane rupture on the day of operation. None of the observed adverse events were product-related fatal events.

[Summary of safety results in Japanese and foreign literature]
Information on adverse events was extracted from all 29 submitted Japanese and foreign documents.

Table 8. List of adverse events

Adverse events	Reference No.	
	Foreign	Japan
Occlusion	1, 5	15, 18, 20, 21, 24
Catheter dislodgement (within the uterus)	1, 10	15, 19
Catheter dislodgement (within the fetal pleural cavity)	1, 8, 10	15, 19, 20, 17, 24, 26
Dislodgement within the abdominal wall of the mother		20
Placement within the muscle layer of the uterine anterior wall		23
Extrauterine placement		23
Migration into the vesicouterine pouch		24
Migration into the uterine wall of the mother		24
Premature rupture of membranes	1, 10	19, 24
Premature rupture of membranes within 4 weeks after shunt tube placement		15
Pneumothorax	10	20, 23
Injury to vasculature in the fetal pleural cavity	8, 9	
Chorioamnionitis	10	

Table 9. Incidence of adverse events

Literature		No. of subjects undergoing shunting	No. of subjects with adverse events (incidence)	Adverse events (complication)
Japan	15	14	2 (14%)	Dislodgement into the fetal pleural cavity
			2 (14%)	Occlusion
			1 (7%)	Dislodgement within the uterus
			4 (29%)	Premature rupture of membranes within 4 weeks after shunt tube placement
	17	1	1 (100%)	Dislodgement within the fetal pleural cavity
	18	8	2 (25%)	Occlusion
	19	11	1 (9%)	Premature rupture of membranes
			1 (9%)	Dislodgement within the uterus
			1 (9%)	Dislodgement within the fetal pleural cavity
	20	2	1 (50%)	Dislodgement within the fetal pleural cavity
			1 (50%)	Dislodgement within the peritoneal cavity
			1 (50%)	Occlusion
			1 (50%)	Pneumothorax
	21	1	1 (100%)	Occlusion
	23	1	1 (100%)	Placement within the muscle layer of the uterine anterior wall
			1 (100%)	Extrauterine placement
			1 (100%)	Pneumothorax
	24	9	2 (22%)	Premature rupture of membranes
			1 (11%)	Dislodgement within the fetal pleural cavity
			1 (11%)	Migration into the vesicouterine pouch
			1 (11%)	Migration into uterine wall of the mother
			1 (11%)	Occlusion
	26	1	1 (100%)	Dislodgement within the fetal pleural cavity

Literature		No. of subjects undergoing shunting	No. of subjects with adverse events (incidence)	Adverse events (complication)
Foreign	1	88	9 (10%)	Occlusion
			5 (6%)	Premature rupture of membranes
			4 (5%)	Dislodgement within the uterus
			1 (1%)	Dislodgement within the fetal pleural cavity
	5	1	1 (100%)	Occlusion
	8	3	1 (33%)	Injury of vasculature in the fetal pleural cavity
			3 (100%)	Dislodgement within the fetal pleural cavity
	9	19	1 (5%)	Injury of vasculature in the fetal pleural cavity
	10	54	5 (9%)	Chorioamnionitis
			9 (17%)	Premature rupture of membranes
			9 (17%)	Pneumothorax
			1 (2%)	Dislodgement within the fetal pleural cavity
			1 (2%)	Dislodgement within the uterus

Adverse events observed after fetal shunting with the proposed product were classified into those observed in maternal bodies, those observed in fetuses, and those observed in newborns, and were extracted from the submitted literature. Adverse events observed in maternal bodies were catheter dislodgement (within the uterus), dislodgement within the abdominal wall of the maternal body, placement within the muscle layer of the uterine anterior wall, extrauterine placement, migration into the vesicouterine pouch, migration into uterine wall of maternal body, premature rupture of membranes, and premature rupture of membranes within 4 weeks after shunt tube placement. Adverse events observed in fetuses were occlusion, catheter dislodgement (within the fetal pleural cavity), and injury to vasculature in the fetal pleural cavity. Pneumothorax was reported as an adverse event observed in newborns.

PMDA evaluated the appropriateness of the clinical evaluation of the proposed product based on the submitted data as shown below, taking account of (1) the public knowledge of fetal shunting for fetal pleural effusion in foreign countries, (2) the extrapolation of foreign clinical data to the Japanese population, and (3) the safety evaluation based on Japanese and foreign literature.

(1). Public knowledge of fetal shunting for fetal pleural effusion in foreign countries

PMDA considered the public knowledge of fetal shunting for fetal pleural effusion in foreign countries as described below:

Since Seed et al. reported fetal shunting in 1986 as a treatment for fetuses with severe fetal pleural effusion, for which the proposed product is intended, the treatment has been performed in many patients. In the present application, the applicant explained the public knowledge of the treatment using 14 foreign documents, including the UK guideline on fetal shunting. Among the submitted foreign literature, literature 4 and 12 are systematic reviews and literature 2 and 3 are nonsystematic reviews. All these reports reviewed the results of interventional treatments including fetal shunting for fetal pleural effusion and reached the conclusions as summarized below: (a) although spontaneous recovery of a fetal pleural effusion occurs in a certain percentage of patients, severe cases have a poor outcome with a survival rate of 23.5% to 35% in those with hydrops; (b) interventional treatment is justified in severe cases; (c) fetal shunting is the most widely used interventional treatment with the post-shunt survival rate being 44% to 66% for cases with hydrops; (d) failure in shunt placement, shunt dislocation, dislodgement, etc., were observed as adverse events; (e) the optimal treatment differs depending on the gestational age, severity, etc., requiring careful evaluation of the indication, and the treatment should be performed by a specialist; and (f) the evidence of interventional treatment for fetal pleural effusion is limited, and high-level evidence from randomized studies is not available from literature. Therefore, the accuracy and quality of the data of interventional studies conducted so far is not high enough. The NHS guidance (2006), which stated that the efficacy and safety of fetal shunting have been

established based on a review of published literature available at that time, pointed out that informed consent should be obtained from family members and that the treatment should be given by a specialist at a specialized institution because there are uncertainties about the natural course of fetal pleural effusion and patient selection. PMDA considered that the above results are valid in confirming that fetal shunting in fetal pleural effusion has a definite clinical role in foreign countries, particularly in severe cases such as those with hydrops. Therefore, it was unnecessary to conduct a prospective clinical study provided that these overseas results can be extrapolated to the Japanese population.

(2). Extrapolation of foreign clinical data to Japanese population

PMDA made the following considerations regarding extrapolation of device use in the Japanese population based on foreign clinical data, as described below:

The Japan Society of Fetal Therapy published the results of a retrospective survey on fetal shunting performed in Japan during the period from 2002 through 2006, in which 71 cases were reported during the 5-year period. Although patient background characteristics and inclusion criteria varied because it was a retrospective survey, the survival rate was shown to be 59%. This suggested that there is no significant difference in the fetal survival rate between Japanese and foreign clinical studies, when consideration is given to the fact that most foreign clinical studies were also retrospective observational studies. In addition, submitted data included the results of a prospective study that was conducted under the Evaluation System of Investigational Medical Care, using only those patients who met the established inclusion/exclusion criteria. The results showed the survival rate of 79.2% in treated patients overall and 70.6% in patients with hydrops. These results are more favorable compared with those of foreign studies and the retrospective study conducted in Japan. It is expected that improved results will be obtained if patient selection, placement procedure, and postoperative management are standardized.

Based on the above, PMDA considered that, although results of clinical studies in Japan are limited, there are no significant differences in the results between those obtained in Japan and those obtained in foreign clinical studies, allowing the extrapolation of foreign study results to the Japanese population. Also, favorable results were obtained in the prospective study, suggesting that it is necessary, as pointed out by the NHS guideline, that patients be selected appropriately, that expert knowledge is critical to avoid adverse events, and that the treatment should be performed by a specialist at a well-equipped institution. Although the intended patients are those with primary fetal pleural effusion as a rule, the treatment is also expected to be sufficiently effective for secondary pleural effusion if the abnormality is limited within the pleural cavity, such as in pulmonary sequestration. Therefore, PMDA considers that it is appropriate that the proposed product is used for such cases after careful assessment by the physician.

(3). Safety evaluation based on Japanese and foreign literature

PMDA evaluated the safety of the proposed product as follows:

All adverse events that occur in the maternal body following fetal shunting appear to be related to the shunting procedure. Therefore, the shunting procedure under ultrasonic guidance should be performed by, or under the guidance of, a skilled physician.

Among adverse events that occur in fetuses, catheter dislodgement is considered to be a certain level of risk for both mothers and fetuses. PMDA asked the applicant about the measures that are necessary in the event of dislodgement. The applicant responded that: (a) in the event of dislodgement within the fetus, the position of the shunt tube should be confirmed by ultrasonography after birth and removed surgically or endoscopically; (b) in the event of dislodgement within the amniotic cavity, the shunt tube may be excreted out of the body at birth together with amniotic fluid. If not, the shunt tube remaining within the uterus should be removed using a hysteroscope and/or ultrasonography.

The management of physical conditions of newborns who underwent fetal shunting should be performed at an institution that can appropriately manage the conditions to reduce the risk of adverse events such as pneumothorax that are associated with shunt tube placement.

Based on the above, PMDA concluded that the safety of the proposed product is acceptable under the conditions that information on frequently-reported shunt tube-related adverse events after the use of the proposed product (dislodgement, occlusion, premature rupture of membranes, haemorrhage caused by centesis) should be provided in the package insert and that shunting should be performed by a specialist in a well-controlled system that is capable of reducing risks and promptly taking appropriate measures if adverse events occur.

Thus, based on the results of the literature review that was submitted as a clinical evaluation of the proposed product and on the results of the Expert Discussion, PMDA accepted the data pertaining to the clinical evaluation.

6. Risk analysis

Documents on the organization for risk management based on JIS T 14971, SOP-related data, and data showing the implementation status of risk analysis were submitted. Until now, there have been no reports of hazards caused by similar medical devices that led to implementation of safety measures required by the MHLW or foreign regulatory agencies.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process

Data on the following information were submitted: manufacturing process and manufacturing sites, sterilization method, and quality control.

PMDA reviewed and accepted the data on the manufacturing process.

IV. Results of Compliance Assessment by PMDA Concerning the Data Submitted in the New Medical Device Application and Conclusion by PMDA

[PMDA's conclusion on the results of document-based compliance assessment]

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application. No particular problems were noted. Thus, PMDA concluded that there should be no problems with conducting a regulatory review based on the submitted product application documents.

[**PMDA's conclusion on the results of the QMS document-based and on-site inspection]**

A compliance review was conducted in accordance with the provision of Paragraph 6 of Article 14 of the Pharmaceutical Affairs Act. PMDA concluded that there were no particular problems.

V. Overall evaluation

The proposed product is composed of a shunt tube to be placed in the fetal pleural cavity under ultrasonic guidance and a delivery system for the tube, for the purpose of continuously draining TC-unresponsive fetal pleural effusions into the maternal amniotic cavity. Data submitted for clinical evaluation of the proposed product comprised foreign literature, Japanese clinical experience, and results of a clinical study in Japan on the efficacy and safety in fetal shunting in patients with fetal pleural effusion. The important point in the review was whether or not the efficacy and safety of the proposed product in Japan could be evaluated based on the limited information. PMDA's conclusions, taking account of comments raised in the Expert Discussion, are stated below.

PMDA performed the review considering (1) the public knowledge of fetal shunting for fetal pleural effusion in foreign countries, (2) the extrapolation of foreign clinical data to the Japanese population, and (3) the safety evaluation based on Japanese and foreign literature.

In regards to the public knowledge of fetal shunting for fetal pleural effusion in foreign countries, PMDA considers that fetal shunting for severe fetal pleural effusion was proven to be effective to a certain extent in foreign countries, taking account of the submitted systematic and non-systematic reviews and the guideline for fetal shunting in the UK that demonstrated (i) interventional treatment is justified for fetuses with severe pleural effusion, (ii) fetal shunting is the most frequently used interventional treatment for severe pleural effusion with recurrence after TC, (iii) survival rates ranged from 44% to 66% in fetuses who received fetal shunting for pleural effusion associated with hydrops, and (iv) the efficacy and safety of fetal shunting have been established according to the UK guideline for fetal shunting.

However, since these results in foreign studies were obtained using products that are different from the proposed product, it is necessary to confirm that the foreign clinical data can be extrapolated to the Japanese population. PMDA has confirmed that the survival rate of newborns in the retrospective survey conducted by the Japan Society of Fetal Therapy was comparable to that observed in the foreign studies. Also, the results of the prospective clinical study conducted in Japan under the Evaluation System of Investigational Medical Care have suggested that improved results will be obtained if patient selection, placement procedure, and postoperative management are standardized. Based on the above, PMDA concluded that the treatment effect achieved by using the proposed product in Japan would not be significantly different from that observed in foreign countries.

In regards to the safety evaluation, PMDA has concluded, after reviewing the Japanese and foreign literature, that information on treatment-related adverse events should be provided appropriately in the package insert and that the shunting should be performed with full informed consent by a specialist in a well-controlled system that is capable of reducing risks and can promptly take appropriate measures in the case of adverse events.

Based on the above, PMDA has concluded that the clinical efficacy and safety can be evaluated based on the submitted clinical evaluation data. Since fetal pleural effusion is a rare disease and it is difficult to accumulate data from limited number of cases, there are uncertainties about the natural course and patient selection and it is necessary to take appropriate measures for adverse events. Therefore, the conditions for approval, 1 and 2 as described below, are imposed so that the treatment is performed by a specialist at a specialized medical institution. In addition, condition 3 is imposed with the aim of further accumulation of case data in Japan, including long-term treatment results.

Based on the review of the above submitted data and by taking account of the comments from the Expert Discussion, PMDA has concluded that the product should be carefully used because of the limited use experience and that the product may be approved for the intended use as described below, because there is no need to use the proposed product in fetuses who can be treated with TC, the commonly used treatment method.

[Intended use]
Fetal Shunt is used to continuously drain the pleural effusion from the fetal pleural cavity into the amniotic cavity when thoracocentesis is not effective.

[Conditions for approval]
The applicant is required to:

1. Take appropriate measures to ensure that the product will be used, in compliance with the indication, by physicians with adequate knowledge/experience in the treatment using the product after acquiring the skills of handling the product and sufficient knowledge of possible complications associated with the procedure by attending relevant training courses or by other means.

2. Take appropriate measures to ensure that the product will be used at well-organized medical institutions staffed with physicians with a thorough knowledge of the treatment for the indicated disease who are fully capable of managing emergencies associated with the use of the product.

3. Register all patients treated with the product during the re-examination period, collect information on the efficacy and safety of the product from the use-results survey, and take appropriate measures as needed.

The product is a medical device with a new method of use and is designated as an orphan medical device. The re-examination period should be 7 years. The product is not classified as a biological product or a specified biological product.

The application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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