November 15, 2023
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Endotoxin removal adsorption hemoperfusion column
Brand Name	Toraymyxin
Applicant	Toray Industries, Inc.
Date of Application	March 31, 2023

Results of Deliberation

In its meeting held on November 15, 2023, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product should be approved with designation as a medical device subject to a use-results survey.

The use-results survey period should be 6 years. The product should be approved with the following underlined conditions.

Approval Conditions

Acute exacerbation of idiopathic pulmonary fibrosis

1. The applicant is required to develop and appropriately implement a medical device risk management plan.
2. The applicant is required to take necessary actions such as dissemination of information, including the proper use standards prepared in cooperation with the related academic society and other relevant information, to ensure that the product is used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of acute exacerbation of idiopathic pulmonary fibrosis after acquiring sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions that have a well-established system for responding to possible complications associated with treatment with the product.
3. The applicant is required to conduct a use-results survey involving all patients treated with the product, periodically report survey results to the Pharmaceuticals and Medical Devices Agency, and promptly take appropriate measures as necessary in cooperation with the related academic society until data from a certain number of patients have been accrued.

Review Report

October 26, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Endotoxin removal adsorption hemoperfusion column
Brand Name	Toraymyxin
Applicant	Toray Industries, Inc.
Date of Application	March 31, 2023 (Application for partial change approval of a medical device)
Items Warranting Special Mention	Priority review Orphan medical device Subject to conditional approval system for medical devices
Reviewing Office	Office of Medical Devices II

Review Results

October 26, 2023

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Endotoxin removal adsorption hemoperfusion column
Brand Name	Toraymyxin
Applicant	Toray Industries, Inc.
Date of Application	March 31, 2023

Results of Review

Toraymyxin (Approval No. 20500BZZ00926000) is an extracorporeal hemoperfusion device intended to selectively adsorb and remove causative agents, mainly endotoxin, in a patient's circulating blood.

The present application for partial change approval for a medical device was submitted to mainly add "improvement in the pathological condition of patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF)" to the intended use of Toraymyxin using the conditional approval system for medical devices.

The present application for partial change approval also proposed extension of therapy duration and a new raw material. The applicant therefore submitted non-clinical data supporting the physicochemical properties and biological safety of Toraymyxin to allow evaluation of the extension of therapy duration and the new raw material. The data showed no particular problem.

The applicant submitted a clinical evaluation report summarizing data from the "Pilot study evaluating the efficacy and safety of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment for idiopathic pulmonary fibrosis with acute exacerbation" (hereinafter referred to as the Advanced Medical Care B Study) and relevant publications. This report was used for clinical evaluation of the efficacy and safety of Toraymyxin in patients with acute exacerbation of IPF.

The Advanced Medical Care B Study showed a 4-week survival rate, the primary efficacy endpoint, of 65.0% (95% confidence interval [CI], 40.3%-81.5%). This result exceeded the maximum survival rate of 40% in patients receiving conventional therapy, which was determined from literature data. The study also suggested improvement in secondary endpoints including oxygenation and chest imaging findings. Although it was exploratory, the study demonstrated the efficacy of Toraymyxin. The outcomes from the other publications are consistent with those of the Advanced Medical Care B Study, indicating a certain level of efficacy of Toraymyxin. For safety, serious adverse events occurred at an incidence of 60.0% (12 of 20 subjects), including cerebral infarction in 1 subject (5.0%), for which a causal relationship to Toraymyxin could not be ruled out. The mortality rate was 50.0% (10 of 20 subjects) during the study period. The cause of death was exacerbation of the underlying disease for all of these subjects, including the aforementioned subject with cerebral infarction. All of the deaths were

causally unrelated to Toraymyxin. It was judged that the cerebral infarction might have been due to procedural air embolism, but this case could have been caused by thromboembolism, etc. associated with worsened general condition due to acute exacerbation of IPF, because the subject had complications (hypertension, etc.) that increase the risk of cerebral infarction. This case calls attention to the potential occurrence of air embolism possibly related to the procedure of Toraymyxin therapy. However, the study and publications did not reveal any adverse event that was clinically unacceptable when weighed against the seriousness of the disease.

There is a high clinical need for a new treatment for acute exacerbation of IPF because pharmacotherapy is the only treatment option available for patients with acute exacerbation of IPF, and because their prognosis is poor if they do not respond to pharmacotherapy. The currently available clinical data, although limited, support a certain level of efficacy and safety of Toraymyxin. PMDA considers that Toraymyxin can be a useful therapy for patients with inadequate response to conventional therapy, provided that sufficient risk management is implemented based on a medical device risk management plan, including collaboration with the related academic society, according to the conditional approval system.

The risk management system of Toraymyxin should be established to ensure that physicians with adequate experience in the diagnosis and treatment of patients with acute exacerbation of IPF select eligible patients for Toraymyxin therapy and treat them with Toraymyxin at medical institutions with adequate experience in hemoperfusion therapy and a well-established medical care system for the treatment of IPF. Further, the applicant should (a) analyze efficacy and safety data collected through a use-results survey, in cooperation with the related academic society, (b) share analysis results with Pharmaceuticals and Medical Devices Agency (PMDA) in a timely manner, and (c) promptly take additional risk reduction measures, etc. as necessary. These activities are essential to ensure the efficacy and safety of Toraymyxin therapy.

As a result of its review, PMDA has concluded that Toraymyxin may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation. The intended use proposed by the present application is underlined.

Intended Use

Toraymyxin <u>is intended to improve the pathological condition of the following patients:</u>

(1) Patients with a severe pathological condition associated with endotoxemia or suspected gram-negative infection

A severe pathological condition should typically meet at least 2 of the following criteria:

- Body temperature of >38˚C or <36˚C
- Heart rate of >90 beats/min
- Respiratory rate of >20 breaths/min or $PaCO_2$ of <4.3 kPa (32 torr)
- White blood cell count of >12000 cells/mm^3 or <4000 cells/mm^3, or ≥10% stab neutrophils

(2) <u>Patients with acute exacerbation of idiopathic pulmonary fibrosis who have not responded to conventional therapy</u>

Approval Conditions

Acute exacerbation of idiopathic pulmonary fibrosis

1. The applicant is required to develop and appropriately implement a medical device risk management plan.
2. The applicant is required to take necessary actions such as dissemination of information, including the proper use standards prepared in cooperation with the related academic society and other relevant information, to ensure that the product is used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of acute exacerbation of idiopathic pulmonary fibrosis after acquiring sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions that have a well-established system for responding to possible complications associated with treatment with the product.
3. The applicant is required to conduct a use-results survey involving all patients treated with the product, periodically report survey results to the Pharmaceuticals and Medical Devices Agency, and promptly take appropriate measures as necessary in cooperation with the related academic society until data from a certain number of patients have been accrued.

Review Report

October 26, 2023

Product for Review

Classification	Instrument & Apparatus 07, Organ Function Replacement Device
Term Name	Endotoxin removal adsorption hemoperfusion column
Brand Name	Toraymyxin
Applicant	Toray Industries, Inc.
Date of Application	March 31, 2023
Proposed Intended Use (Underline denotes additions.)	1. Intended Use Toraymyxin is a hemoperfusion device intended to selectively adsorb and remove causative agents, mainly endotoxin, in circulating blood through whole blood hemoperfusion. Toraymyxin contains polymyxin B-immobilized polystyrene derivative (chloroaceto-amidomethylated polystyrene) fibers. The immobilized polymyxin B on the fibers selectively adsorbs and removes endotoxin in the patient's blood. 2. Indications Toraymyxin is intended to improve the pathological condition of patients with a severe pathological condition associated with endotoxemia or suspected gram-negative infection. A severe pathological condition should typically meet at least 2 of the following criteria: • Body temperature of >38˚C or <36˚C • Heart rate of >90 beats/min • Respiratory rate of >20 breaths/min or $PaCO_2$ of <4.3 kPa (32 torr) • White blood cell count of >12000 cells/mm^3 or <4000 cells/mm^3, or ≥10% stab neutrophils Toraymyxin is intended to treat patients with acute exacerbation of idiopathic pulmonary fibrosis in order to improve their pathological condition.

Items Warranting Special Mention

Priority review
Orphan medical device
Subject to conditional approval system for medical devices

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List of Abbreviations

$AaDO_2$	Alveolar-arterial Oxygen Difference
ARDS	Acute Respiratory Distress Syndrome
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DAD	Diffuse Alveolar Damage
FiO_2	Fraction of inspiratory Oxygen
HRCT	High Resolution CT
IL	Interleukin
IPF	Idiopathic Pulmonary Fibrosis
KL-6	Sialylated Carbohydrate Antigen Krebs von den Lungen-6
LDH	Lactate Dehydrogenase
$PaCO_2$	Arterial Partial Pressure of Carbon Dioxide
PaO_2	Arterial Partial Pressure of Oxygen
P/F	PaO_2/FiO_2
PMX	Polymyxin B-immobilized fiber column
SP-A, SP-D	Surfactant Protein-A, -D

I. Product Overview

Toraymyxin is an extracorporeal hemoperfusion device intended to selectively adsorb and remove causative agents, mainly endotoxin, in a patient's circulating blood. The case contains antibiotic polymyxin B-immobilized polystyrene-derivative fiber. The immobilized polymyxin B on the fibers selectively adsorbs and removes endotoxin in a patient's blood (Figure 1, Table 1).

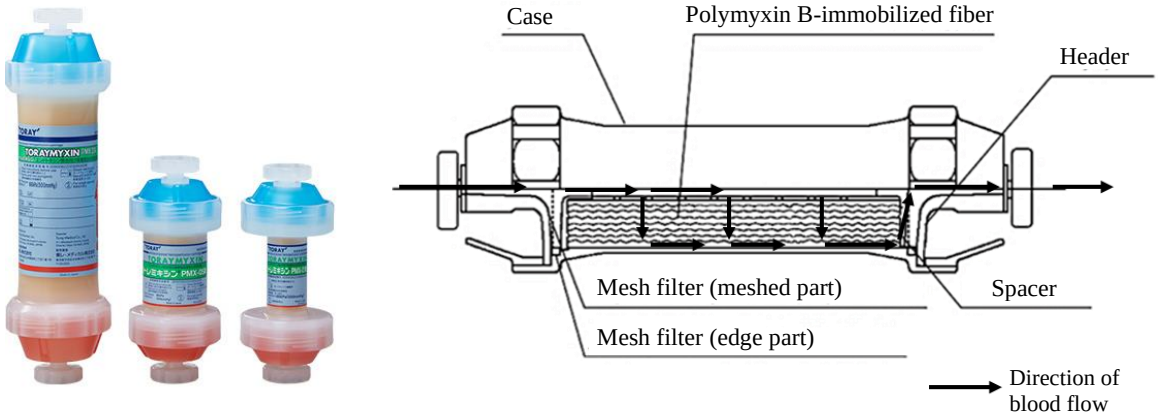

Figure 1. Appearance and structure of Toraymyxin

Table 1. Size of Toraymyxin

	PMX-01R	PMX-05R	PMX-20R	[redacted]
Length (mm)	133	133	225	[redacted]
Maximum diameter (mm)	55	55	63	[redacted]
Housing diameter (mm)	25	40	49	[redacted]
Blood volume (mL)	8.0 ± 2.5	40 ± 3	135 ± 5	[redacted]
[redacted]				

Toraymyxin was approved on October 27, 1993 for the intended use "Improvement in the pathological condition of patients with a severe pathological condition associated with endotoxemia or suspected gram-negative infection (sepsis)" (hereinafter referred to as the approved indication) (Approval No. 20500BZZ00926000).

The present application for partial change approval (hereinafter referred to as the present partial change application) is mainly intended to add "improvement in the pathological condition of patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF)" (hereinafter referred to as the expanded indication) to the intended use of Toraymyxin. In order to improve the supply stability of Toraymyxin, the present partial change application is also intended to add a new raw material of [redacted] of the mesh filter, which is a component of Toraymyxin that removes floating substances and fine fibers from the blood flow passage.

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

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

The expert advisors present during the Expert Discussion on Toraymyxin declared that they did not fall under the Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Idiopathic interstitial pneumonia is a type of fibrosing interstitial pneumonia that causes inflammation and injury of the lung interstitium, without any known cause. It is classified as a designated intractable disease[1] by the Ministry of Health, Labour and Welfare (MHLW). In idiopathic pulmonary fibrosis (IPF), which has the worst prognosis among the types of idiopathic interstitial pneumonia,[2] pulmonary fibrosis progresses from the subpleural lower lung zones and results in the irreversible honeycomb lungs. IPF is a chronic disease with progressive respiratory dysfunction. Its average survival is reportedly 3 to 5 years after definitive diagnosis.[1] IPF is basically irreversible and progressive. First-line drugs for the treatment of IPF to prevent its progression are anti-fibrotic drugs: Pirfenidone (brand names "Pirespa Tables 200 mg" and others) and nintedanib ethanesulfonate (brand names "Ofev Capsules 100 mg" and "Ofev Capsules 150 mg").[3]

"Acute exacerbation of IPF" is a pathological condition where respiratory failure progresses acutely during the chronic course of IPF, accompanied by the presence of new infiltrative shadows in both lung fields. The cause and mechanism of acute exacerbation of IPF remain unknown.[3] Histopathology shows (a) the signs of usual interstitial pneumonia, which characterize IPF and (b) diffuse alveolar damage (DAD), which characterizes acute respiratory distress syndrome (ARDS) causing severe respiratory failure. Acute exacerbation occurs in approximately 5% to 15% of patients with IPF per year, and is the most common cause of death in IPF, accounting for 40% of deaths from IPF.[3] The prognosis of patients with acute exacerbation of IPF is very poor with an average survival of ≤2 months.[2] The "Japanese Guideline for the Treatment of Idiopathic Pulmonary Fibrosis 2017"[4] "suggests" pharmacotherapy (e.g., steroids, immunosuppressants, neutrophil elastase inhibitors, anti-fibrotic agents) or direct hemoperfusion with Toraymyxin (hereinafter referred to as Toraymyxin therapy) to treat acute exacerbation of IPF.

Toraymyxin has been used to treat patients with septic shock caused by gram-negative bacteria. Since around 2002, Toraymyxin therapy has been reported to improve oxygenation and circulatory dynamics in ARDS resulting from sepsis (one of the underlying conditions of ARDS) and have the potential to improve survival rates.[5,6,7] With the expectation that Toraymyxin could be effective in the treatment of acute exacerbation of IPF with DAD, which is the major pulmonary histopathological sign of ARDS, Toraymyxin has been used in clinical practice to treat acute exacerbation of IPF since approximately 2004. Some reports from clinical practice described the efficacy outcomes of Toraymyxin, including improvement in oxygenation.[8,9,10] In the Research Project on Rare and Intractable Diseases sponsored by the Ministry of Health, Labour and Welfare titled "Research on the Diffuse Lung Diseases,"[11] a nationwide multicenter, retrospective, comprehensive study was conducted from 2008 to evaluate the clinical effects of Toraymyxin on acute exacerbation of IPF. The study enrolled 160 patients with acute

exacerbation of progressive interstitial pneumonia including IPF (including 73 patients with IPF) at 18 medical institutions in Japan. In the study, Toraymyxin therapy resulted in a significant improvement in oxygenation and a significant reduction in white blood cell count in peripheral blood. The 4-week survival rate was 70.1% and the 12-week survival rate was 34.5%. These treatment outcomes were favorable and suggested greater improvement in the prognosis of acute exacerbation of IPF than did data from previous reports.

On the basis of these results, Toraymyxin therapy was designated as Advanced Medical Care B "polymyxin B-immobilized fiber column (PMX) hemoperfusion therapy; idiopathic pulmonary fibrosis (limited to acute exacerbation)." An investigator-initiated clinical research "Pilot study evaluating the efficacy and safety of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment for idiopathic pulmonary fibrosis with acute exacerbation" (hereinafter referred to as the Advanced Medical Care B Study) was conducted from 2014 to 2018.

The results of the Advanced Medical Care B Study prompted the Japanese Respiratory Society to submit a written request for early regulatory approval of Toraymyxin for the expanded indication in February 2019. In August 2021, Toraymyxin was designated as an orphan medical device to be used for the expanded indication.

1.A.(2) Applicability of conditional approval system for medical devices

The conditional approval system for medical devices is intended to approve medical devices meeting both of the following criteria:

(a) Intended to be used for the treatment of diseases that significantly affect patients' lives and have no effective therapy.
(b) Collecting clinical data required for approval application is extremely difficult because, for example, conducting a clinical study takes a considerable time due to a limited number of patients.

This system was introduced to promote early introduction of such medical devices into clinical practice while maintaining a risk-benefit balance on the following premises:

(a) A post-marketing risk management plan, including establishment of use conditions and post-marketing data collection, should be drafted in the development stage.
(b) Stringent measures should be taken to address risks that cannot be identified from the limited clinical data available before application.

In response to designation of Toraymyxin as an orphan medical device, the applicant submitted the present partial change application after the Medical Device Evaluation Division of the MHLW presented their view that the proposed expanded indication of Toraymyxin could be reviewed through the conditional approval system for the reasons shown in Table 2.

Table 2. MHLW's Judgement regarding applicability of conditional approval system to Toraymyxin

Requirements*	Reasons Toraymyxin meets requirements for conditional approval system
1	The most common cause of death in IPF is acute exacerbation, accounting for 40% of deaths from IPF. The prognosis of patients with acute exacerbation of IPF is very poor, with an average survival period of ≤2 months and a survival rate of approximately 20% after the first acute exacerbation.
2	No drug or medical device is indicated for the treatment of acute exacerbation of IPF. No effective standard therapy has been established.
3	The results of the Advanced Medical Care B Study demonstrated a certain level of efficacy and safety of Toraymyxin.
4	In Japan, acute exacerbation of IPF is a rare disease, occurring in approximately 1,000 patients per year. Approximately 200 to 300 patients per year at maximum are estimated to receive Toraymyxin therapy.[12] It is difficult to conduct a new clinical study of Toraymyxin because many patients with IPF have advanced age or have concurrent lung cancer, and obtaining consent for participation in a clinical study from patients with acute exacerbation is challenging because the timing of treatment is limited due to the acute nature of this condition. It took 3.5 years to enroll 20 patients at 2 study sites in the Advanced Care B Study.
5	The Diffuse Lung Disease Assembly of the Japanese Respiratory Society has agreed to cooperate in drafting proper use standards of Toraymyxin. The applicant has consulted with PMDA about the details of the medical device risk management plan, including a use-results survey.

* Requirements (Category 1):

1. The disease significantly affects the patient's life, or is irreversible and substantially affects the patient's daily life activities.
2. No therapy, preventive method, or diagnostic method exists for the disease, or the proposed product is expected to have significantly higher efficacy or safety than conventional therapies, etc.
3. Enough clinical data are available for a certain level of evaluation.
4. Conducting a new clinical study or clinical performance study is very difficult. The difficulty can be explained in a rational way.
5. Proper use standards can be prepared in close cooperation with the related academic society. A specific plan for post-marketing data collection and evaluation is available.

1.A.(3) Use in foreign countries

Toraymyxin is not approved for the treatment of acute exacerbation of IPF outside Japan. Table 3 presents the approved indication and sales information of Toraymyxin as of [redacted] 2023 outside Japan. Toraymyxin is not approved in the US.

A total of [redacted] units of Toraymyxin were sold worldwide between the market launch in October 1993 and [redacted] 2023.

Table 3. Approved indication and sales information in EU

Country/region	Approved intended use	Market launch	Sales quantity
EU	Toraymyxin is a hemoperfusion column intended for the selective adsorption and removal of causative agents, mainly endotoxin, in circulating blood through whole blood hemoperfusion.	2001	[redacted]

1.A.(4) Malfunctions and adverse events in and outside Japan

Table 4 and Table 5 present adverse events in patients who used Toraymyxin for the approved indication that were reported to the regulatory authorities in and outside Japan, respectively, by August 2023.

Table 4. Adverse events in Japan (the approved indication)

Adverse event	Number of events	Incidence*
Blood pressure decreased	[redacted]	0.0025%
Platelet count decreased	[redacted]	0.0012%
Allergy, shock, anaphylactic shock	[redacted]	0.0025%
Ventricular tachycardia	[redacted]	0.0009%
Nausea, vomiting	[redacted]	0.0009%
Heart rate increased	[redacted]	0.0003%
Arterial blood oxygen saturation decreased	[redacted]	0.0003%
Respiratory arrest	[redacted]	0.0003%
Muscular weakness	[redacted]	0.0003%
Haemolytic anaemia	[redacted]	0.0003%
Atrial fibrillation	[redacted]	0.0003%
Wheezing	[redacted]	0.0003%
White blood cell count decreased	[redacted]	0.0003%
Pancytopenia	[redacted]	0.0003%
Hepatic function decreased	[redacted]	0.0003%

*Incidence [redacted] (number of units sold in Japan)

Table 5. Adverse events outside Japan (the approved indication)

Adverse event	Number of events	Incidence*
Ventricular tachycardia	[redacted]	0.0034%
Acute renal failure	[redacted]	0.0034%
Neutropenia	[redacted]	0.0034%
Secondary infection	[redacted]	0.0034%

* Incidence [redacted] (number of units sold outside Japan)

1.B Outline of the review conducted by PMDA

All of the adverse events provided in the present application were known events that occurred in patients who used Toraymyxin for the approved indication.

The results from the clinical study described later in Section 6 are the main available clinical data on Toraymyxin therapy for acute exacerbation of IPF in and outside Japan. The clinical study results are reviewed in Section 6. Safety measures to be taken based on the review are described in Section 7.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The present partial change application includes no addition to the current performance specifications of Toraymyxin. Some modification was made to the specifications according to the latest regulations.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the modifications to the performance and safety specifications, and concluded that there was no particular problem.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

The present partial change application proposed to add a new raw material of [redacted] of the mesh filter. To support its chemical properties, the applicant submitted the results of a test using extracts.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data on the physicochemical properties and concluded that there was no particular problem.

2.(3) Biological safety

2.(3).A Summary of the data submitted

The present partial change application proposed new duration of use (i.e., ≥6 hours, up to 24 hours, per cartridge) for the proposed expanded indication (the duration of use for the approved indication is 2 hours). Further, up to 3 cartridges can be used for the proposed expanded indication. Accordingly, Toraymyxin is classified as a "medical device that connects the inside and outside of the body and comes into contact with the circulating blood for a short or medium period of time (>24 hours and ≤30 days)." The present application also proposed to add a new raw material of [redacted] of the mesh filter. For these reasons, the applicant submitted the results of cytotoxicity, skin sensitization, irritation/intradermal reaction, pyrogenicity, acute systemic toxicity, sub-acute systemic toxicity, genotoxicity, and blood compatibility tests. These tests showed no problematic findings.

No implantation test of Toraymyxin was conducted because the other tests demonstrated no risk of short- or medium-term local abnormalities, and because no adverse events associated with local pathological abnormalities (e.g., vascular capsular formation, degeneration, and necrosis) occurred in patients who used Toraymyxin in clinical practice for the approved indication or in subjects of the Advanced Medical Care B Study.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data on biological safety and concluded that there was no particular problem.

2.(4) Mechanical safety

2.(4).A Summary of the data submitted

[redacted] of the mesh filter, a new raw material proposed in the present partial change application, is processed into a mesh filter of the same form [redacted] as the current one. This means that there is no change that might affect the mechanical safety (e.g., pressure resistance and leakage) of Toraymyxin. The applicant therefore did not submit data on the mechanical safety.

2.(4).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of data since the design of Toraymyxin has not been changed.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

Since the present partial change application proposed to add a new raw material of [redacted] of the mesh filter, the applicant submitted the data on stability. Toraymyxin requires no special storage conditions. There is no change in the raw materials, other than that of the mesh filter. The quality of the raw material of the mesh filter is not compromised over time. For these reasons, the applicant omitted the submission of stability data for determining shelf life and instead submitted a self-declaration stating

that the shelf life of Toraymyxin was determined based on necessary stability evaluation, in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability, and concluded that there was no particular problem.

2.(6) Performance and directions for use

2.(6).A Summary of the data submitted

Since the present partial change application includes no change in the polymyxin B-immobilized fiber used to adsorb endotoxin, etc., or in the instructions for use, the applicant did not submit data on the performance and instructions for use of Toraymyxin.

2.(6).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of data since there is no change in the performance and instructions for use of Toraymyxin.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that Toraymyxin 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 Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Toraymyxin to the Essential Principles.

(1) PMDA's view on the conformity of Toraymyxin to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," selection of eligible patients, users, and medical institutions for Toraymyxin therapy, provision of relevant information to users, and compliance with proper use standards are important to maintain a risk-benefit balance of Toraymyxin. To this end, approval conditions should be imposed to ensure that necessary actions are taken.

(2) PMDA's view on the conformity of Toraymyxin to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," the efficacy and safety of Toraymyxin must be

evaluated in clinical use in Japan since the clinical efficacy and safety data of Toraymyxin used for the proposed expanded indication are limited. PMDA instructed the applicant to develop a risk management system and conduct a use-results survey based on a medical device risk management plan.

(3) PMDA's view on the conformity of Toraymyxin to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," the Advanced Medical Care B Study demonstrated a certain level of efficacy and safety of Toraymyxin. Toraymyxin conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of Toraymyxin to Article 4, which stipulates the shelf-life or durability of medical devices:
As described earlier in Section 2.(5), the applicant submitted the self-declaration stating that the shelf life of Toraymyxin was determined based on the results of necessary stability studies in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). Toraymyxin conforms to Article 4.

(5) PMDA's view on the conformity to Article 7, which stipulates the chemical, biological safety, etc. of medical devices:
As described in Sections 2.(2) and 2.(3), Toraymyxin has been shown to have a favorable biological safety. Toraymyxin conforms to Article 7.

(6) PMDA's view on the conformity of Toraymyxin to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions, etc.):
As described later in Section "6.B Outline of the review conducted by PMDA" and Section "7.B Outline of the review conducted by PMDA," it is essential for users to fully understand the risks of Toraymyxin, select patients eligible for Toraymyxin therapy, and use Toraymyxin properly in order to maintain its risk-benefit balance. To this end, relevant information should be provided through the Information on Precautions, etc., proper use standards, and other measures.

PMDA comprehensively reviewed the conformity of Toraymyxin to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971: 2019 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA reviewed the document on risk management taking into account the discussion presented in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

Since the present partial change application includes no change in the manufacturing process, the applicant did not submit data on the manufacturing process.

5.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of the data.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted a clinical evaluation report summarizing the data from the Advanced Medical Care B Study and relevant publications, to support clinical evaluation of Toraymyxin.

6.A.(1) Advanced Medical Care B Study (Study period 2014 to 2018)

As shown in Table 6, the Advanced Medical Care B Study was a multicenter, prospective, single-arm clinical study conducted at 2 study sites in Japan to evaluate the efficacy and safety of Toraymyxin therapy added on to conventional pharmacotherapy (i.e., combination of steroid pulse therapy, neutrophil elastase inhibitors, and immunosuppressants) in patients with acute exacerbation of IPF.

Table 6. Outline of the Advanced Medical Care B Study

Item	Outline
Objectives	To evaluate the efficacy and safety of Toraymyxin therapy added on to conventional pharmacotherapy (combination of steroid pulse therapy, neutrophil elastase inhibitors, and immunosuppressants) in patients with acute exacerbation of IPF
Type of the study	Non-randomized, open-label, multicenter, exploratory study
Study population	Patients with acute exacerbation of IPF
Major inclusion criteria	• Patients aged ≥20 and <80 years at the time of consent • Patients with all of the following conditions within 1 month during the course of IPF: ➢ Increased dyspnea ➢ New ground-glass opacity or infiltrative shadows in addition to a honeycomb lung(s) on chest imaging (high resolution CT [HRCT] findings in principle) ➢ Decreased arterial partial pressure of oxygen (PaO_2) (PaO_2 ≥10 mmHg under the same conditions) • Patients with PaO_2/FiO_2 ratio (P/F ratio) <300 at enrollment
Major exclusion criteria	• Patients who are participating in a clinical study of another unapproved medical device or drug; or patients who participated in a clinical study of an unapproved drug and the period that has passed since the end of study treatment is <5 times as long as the blood half-life of the unapproved drug. • Patients with conditions that hinder appropriate evaluation in the study, such as terminal cancer, chronic renal failure, and life expectancy of ≤7 days • Patients with endotoxemia • Patients with clinically diagnosed clear lung infection, pneumothorax, pulmonary embolism, or heart failure
Sample size	20 patients
Rationale for the sample size	The lower limit of the 95% CI in 20 subjects is 39% assuming a 4-week survival rate of 60% in patients treated with Toraymyxin, which was determined from published data.[13] The 4-week survival rates for the conventional therapy are reportedly 10% to 40%.[11,14] Their upper limits are almost equal to the lower limit of the 95% CI with Toraymyxin. The superiority of Toraymyxin to conventional therapy could be evaluated in 20 subjects.
Directions for use	All enrolled subjects received Toraymyxin therapy in addition to conventional pharmacotherapy (combination of steroid pulse therapy, neutrophil elastase inhibitors, and immunosuppressants). Toraymyxin therapy was administered at a flow rate of 60 to 100 mL/min with an anticoagulant (nafamostat mesylate 30 mg/h). This treatment required at least 2 cartridges of Toraymyxin (whether to use the third cartridge was decided by the investigator).
Observation period	12 weeks after the start of Toraymyxin therapy
Primary endpoints	*Efficacy endpoint* 4-week survival rate after the start of Toraymyxin therapy (Kaplan-Meier's estimate) *Safety endpoint* The symptoms, date of onset, severity, seriousness, predictability, and a causal relationship to Toraymyxin were investigated for each adverse event (including abnormal changes in vital signs, laboratory tests, etc.) occurring between the start of Toraymyxin therapy and the end of observation period (12 weeks after the start of Toraymyxin therapy).
Secondary endpoints	*Efficacy endpoints* 1. Short-term effect on oxygenation • P/F ratio • Alveolar-arterial oxygen difference ($AaDO_2$) 2. Short- and medium-term effect on chest imaging findings • X-ray images or HRCT images 3. Short-term effect on blood CRP 4. Medium-term effect on oxygenation • P/F ratio • $AaDO_2$ 5. Duration of mechanical ventilation 6. 12-week survival rate after the start of Toraymyxin therapy (Kaplan-Meier's estimate)
Exploratory endpoints	Changes in biomarkers and cytokines at the start of Toraymyxin therapy and after the use of 2 cartridges • Biomarkers: KL-6, SP-D, and SP-A • Cytokines: IL-6, IL-8, IL-10, IL-1beta, and IL-17

All of the 20 patients who provided written consent to study participation were enrolled in the study and started Toraymyxin therapy (Figure 2). Ten subjects were withdrawn from the study after the start of Toraymyxin therapy; they could not continue participating in the study because of serious adverse events resulting in death.

All of the enrolled 20 subjects received Toraymyxin therapy at least once and were included in efficacy analysis. Of the 20 subjects, 5 subjects met some exclusion criteria. (The possibility of endotoxemia could not be ruled out because of missing baseline endotoxin data in 4 subjects and pulmonary embolism in 1 subject.) These subjects were included in the efficacy analysis because the possibility of endotoxemia was ruled out in the 4 subjects based on their other measurements and clinical signs suggestive of acute exacerbation of IPF, and because the embolus in the 1 subject was very small and located in the lung periphery.

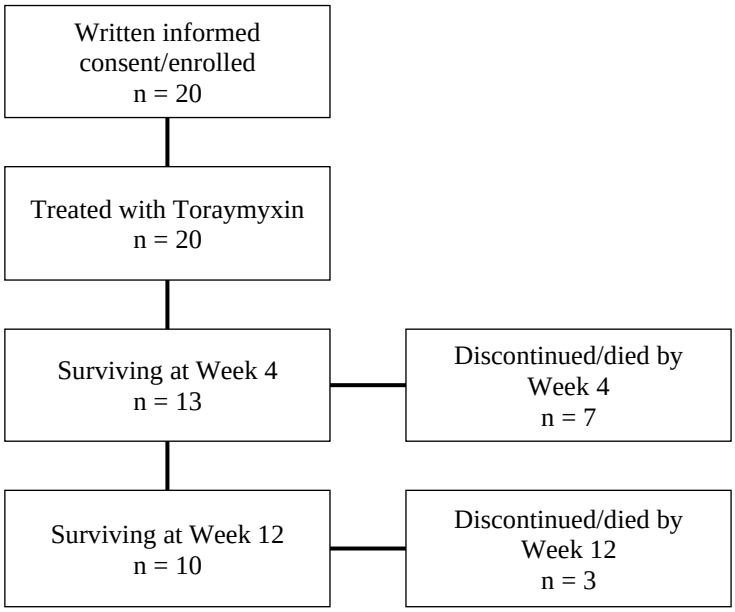

Figure 2. Disposition of subjects

Table 7 presents the characteristics and clinical findings of subjects. Table 8 presents the duration of use and flow rate of Toraymyxin.

Table 7. Patient characteristics and clinical findings

Patient characteristics and clinical findings		Percentage of subjects, mean ± SD, or Min-Max
Sex	Male	90.0% (18/20)
	Female	10.0% (2/20)
Age (years)	Mean ± standard deviation (SD)	66.5 ± 7.09
	Min-Max	51.0-76.0
Age at onset (years)*1	Mean ± SD	62.5 ± 6.5
	Min-Max	49.0-71.0
Type of onset	Chronic (≥3 months)	100.0% (20/20)
	Sub-acute (1-3 months)	0.0% (0/20)
	Acute (≤1 month)	0.0% (0/20)
Prior treatment	Yes	100.0% (20/20)
	No	0.0% (0/20)
Complication	Yes	90.0% (18/20)
	No	10.0% (2/20)
History of smoking	Yes	90.0% (18/20)
	No	10.0% (2/20)
Crepitations	Yes	95.0% (19/20)
	No	0.0% (0/20)
	Unknown	5.0% (1/20)
Dry cough	Yes	95.0% (19/20)
	No	5.0% (1/20)
Dyspnoea exertional	Yes	100.0% (20/20)
	No	0.0% (0/20)
Clubbed finger	Yes	65.0% (13/20)
	No	20.0% (4/20)
	Unknown	15.0% (3/20)
Quantification of endotoxin (immunoserological test)		
Quantitative value (pg/mL)*2	Mean ± SD	1.0 ± 0.2
	Min-Max	0.9-1.3
Positive/negative*3	Positive	5.6% (1/18)
	Negative	94.4% (17/18)

*1 Only subjects with available data (n = 17) were included in the calculation.
*2 Only subjects with available data (n = 3) were included in the calculation.
*3 Only subjects with available data (n = 18) were included in the calculation.

Table 8. Duration of use and flow rate of Toraymyxin

		First cartridge	Second cartridge	Third cartridge
No. of subjects	Percentage	100.0% (20/20)	100.0% (20/20)	45.0% (9/20)
Duration of use (h)	n	20	20	9
	Mean ± SD	14.3 ± 10.0	15.1 ± 13.4	16.1 ± 8.6
	Median	9.1	6.9	21.8
Flow rate (mL/min)	n	20	19	9
	Mean ± SD	81.9 ± 11.7	84.0 ± 10.8	80.9 ± 8.0
	Median	80.0	80.0	80.0

6.A.(1).1) Efficacy evaluation

(a) Primary endpoint: 4-week survival rate after the start of Toraymyxin therapy (Kaplan-Meier's estimate)

The Kaplan-Meier estimate of the 4-week survival rate after the start of Toraymyxin therapy was 65.0% (95% CI, 40.3%-81.5%). The lower limit of the 95% CI exceeded the external reference value (i.e., the maximum 4-week survival rate of 40% for the conventional therapy determined from literature data[11,14]) (Figure 3, Table 9).

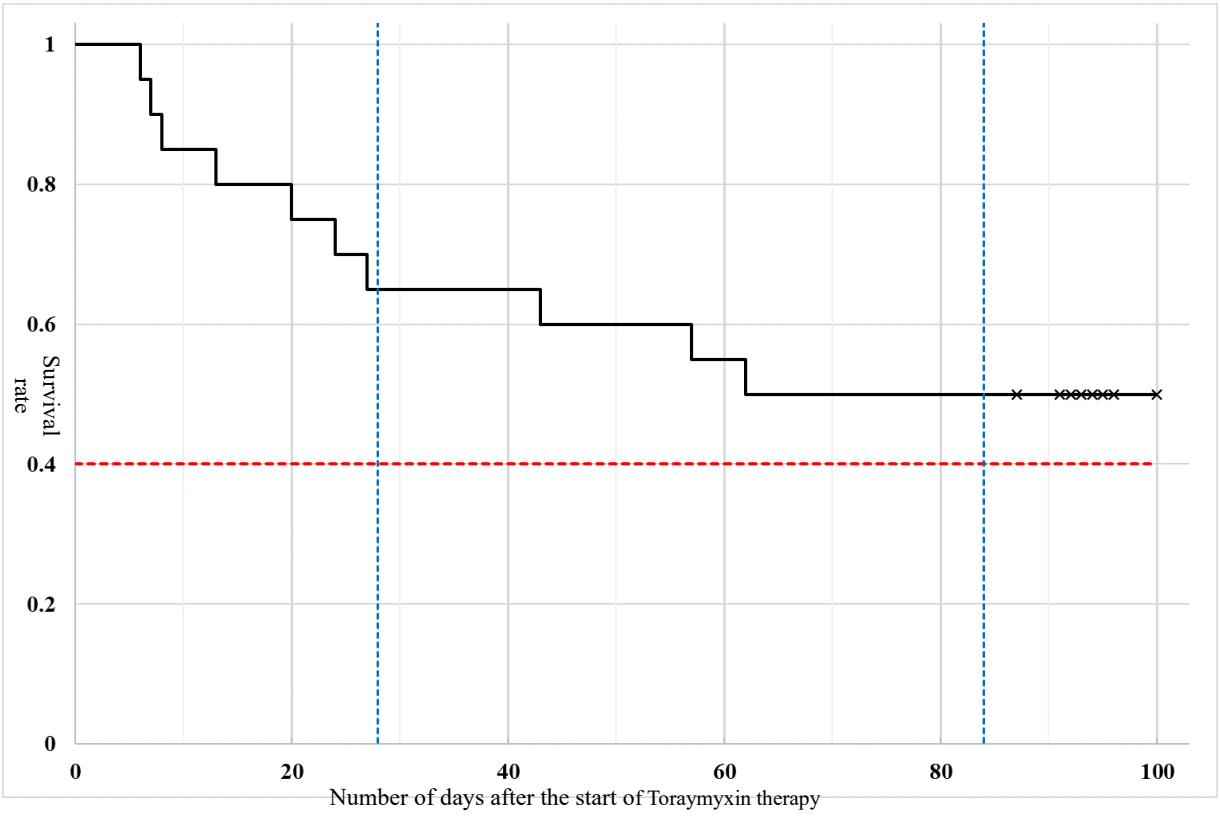

Figure 3. Kaplan-Meier curve of survival rate after the start of Toraymyxin therapy

* Kaplan-Meier estimates are shown in the solid line.
* ✕ indicates a censored case.
* The blue vertical lines indicate 4 weeks (28 days) and 12 weeks (84 days) after the start of Toraymyxin therapy.
* The red horizontal line indicates the external reference value (i.e., the maximum survival rate of 40% after conventional therapy).

Table 9. Survival rate after the start of Toraymyxin therapy

Timing of death (day)	≥6	≥7	≥8	≥14	≥20	≥24	≥27	≥43	≥57	≥62
No. of subjects surviving	20	19	18	17	16	15	14	13	12	11
No. of subjects with event	1	1	1	1	1	1	1	1	1	1
Survival rate	95.0	90.0	85.0	80.0	75.0	70.0	65.0	60.0	55.0	50.0
Upper limit of CI	99.3	97.4	94.9	92.0	88.7	85.3	81.5	77.6	73.5	69.2
Lower limit of CI	69.5	65.6	60.4	55.1	50.0	45.1	40.3	35.7	31.3	27.1

(b) Secondary endpoint: 12-week survival rate after the start of Toraymyxin therapy

The Kaplan-Meier estimate of the 12-week survival rate after the start of Toraymyxin therapy was 50.0% (95% CI, 27.1%-69.2%). The mean survival rate exceeded the external reference value (i.e., the maximum 12-week survival rate of 4% for the conventional therapy determined from literature data[11,14]).

(c) Secondary endpoint: Short- and medium-term effect on oxygenation

The alveolar-arterial oxygen difference ($AaDO_2$) and arterial partial pressure of oxygen (PaO_2)/fraction of inspiratory oxygen (FiO_2) (P/F) ratios during the period of Toraymyxin therapy improved, except for the P/F ratios in the subjects who died by Week 4. Subjects who were surviving at Week 4 maintained the improvement at Week 12 (Table 10, Table 11).

Table 10. Changes in $AaDO_2$ after the start of Toraymyxin therapy

	Baseline	End of first cartridge	End of second cartridge	End of third cartridge	Week 4	Week 12
Subjects surviving at Week 4						
n	13	9	10	3	13	6
Mean ± SD	164.9 ± 85.1	143.2 ± 83.2	115.5 ± 47.1	124.3 ± 37.1	83.2 ± 46.2	81.9 ± 38.9
Median	146.3	142.9	118.7	129.5	68.3	74.4
Mean change from baseline	-	-13.9	-43.1	-87.1	-81.8	-112.5
Subjects who died by Week 4						
n	7	5	6	4	1	0
Mean ± SD	360.3 ± 118.9	297.3 ± 180.2	299.3 ± 125.1	278.2 ± 134.8	599.8	-
Median	312.6	260.6	292.6	280.4	599.8	-
Mean change from baseline	-	-67.4	-69.0	-80.2	+39.0	-

Unit for $AaDO_2$, mmHg

Table 11. Changes in P/F ratio after the start of Toraymyxin therapy

	Baseline	End of first cartridge	End of second cartridge	End of third cartridge	Week 4	Week 12
Subjects surviving at Week 4						
n	13	9	10	3	13	6
Mean ± SD	198.1 ± 66.5	245.6 ± 64.9	261.5 ± 59.6	325.0 ± 15.0	267.9 ± 69.6	256.3 ± 33.6
Median	184.0	253.0	257.0	333.3	262.8	254.2
Mean change from baseline	-	51.1	60.4	160.0	69.8	72.9
Subjects who died by Week 4						
n	7	5	6	4	1	0
Mean ± SD	116.5 ± 50.3	238.5 ± 165.5	194.9 ± 45.7	222.0 ± 69.7	38.2	-
Median	100.1	191.7	192.8	243.3	38.2	-
Mean change from baseline	-	128.1	74.8	116.9	-61.9	-

(d) Secondary endpoint: Short- and medium-term effect on chest imaging findings

The improvement rates based on chest X-ray findings at 24 hours, 72 hours, and 1 week after the end of Toraymyxin therapy, and Weeks 4 and 12 after the start of Toraymyxin therapy were 38.9% (7 of 18 subjects), 50.0% (8 of 16 subjects), 78.6% (11 of 14 subjects), 25.0% (1 of 4 subjects), and 60.0% (3 of 5 subjects), respectively. The improvement rates based on chest high resolution CT (HRCT) findings at 24 hours, 72 hours, and 1 week after the end of treatment, and Weeks 4 and 12 after the start of Toraymyxin therapy were 0.0% (0 of 0 subjects), 50.0% (1 of 2 subjects), 50.0% (1 of 2 subjects), 83.3% (10 of 12 subjects), and 100.0% (4 of 4 subjects), respectively.

(e) Secondary endpoint: Short- and medium-term effect on blood CRP

The change in blood C-reactive protein (CRP) increased with increasing number of Toraymyxin cartridges used. Improvement in blood CRP was observed at the completion of the second and third cartridges. The improvement was maintained up to Week 12 (Table 12).

Table 12. Changes in blood CRP after the start of Toraymyxin therapy

	Baseline	End of first cartridge	End of second cartridge	End of third cartridge	Week 4	Week 12
n	20	16	19	9	14	9
Mean ± SD	7.0 ± 6.8	6.9 ± 6.8	2.8 ± 3.0	3.4 ± 3.2	3.1 ± 5.1	1.2 ± 1.5
Median	4.7	3.5	1.4	2.0	0.4	0.8

Unit for CRP, mg/dL

(f) Duration of mechanical ventilation

Only 2 subjects used mechanical ventilation for 14.0 days (mean duration).

(g) Biomarkers and cytokines

Toraymyxin therapy tended to reduce a biomarker surfactant protein-A (SP-A). The reduced levels, in comparison with baseline, were maintained until Week 4. Surfactant protein-D (SP-D) tended to start decreasing at 24 hours after the end of Toraymyxin therapy. The decrease at Week 4 was statistically significant. Sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6) showed no consistent tendency.

Toraymyxin therapy tended to reduce cytokines interleukin (IL)-6 and IL-8. Changes in IL-10, IL-1beta, and IL-17 could not be assessed because of the limited number of samples.

6.A.(1).2) Safety evaluation

All subjects experienced adverse events. A causal relationship to Toraymyxin could not be ruled out for the following adverse events: Cerebral infarction, hematuria, and epistaxis in 1 subject each (5.0%; 95% CI, 0.13%-24.9%). Serious adverse events occurred in 12 subjects (60.0%). Serious adverse event for which a causal relationship to Toraymyxin could not be ruled out was cerebral infarction in 1 subject (5.0%; 95% CI, 0.13%-24.9%) (Table 13). The cerebral infarction was caused by procedure-related air emboli according to the Independent Review Committee.

Table 13. Summary of serious adverse events

	All events		Moderate*1		Severe*2	
	No. of subjects	%	No. of subjects	%	No. of subjects	%
Total	12	60.0	2	10.0	10	50.0
General disorders and administration site conditions	1	5.0	1	5.0	-	-
Multiple organ dysfunction syndrome	1	5.0	1	5.0	-	-
Infections and infestations	3	15.0	3	15.0	-	-
Pneumonia	3	15.0	3	15.0	-	-
Bacterial infection	1	5.0	1	5.0	-	-
Musculoskeletal and connective tissue disorders	1	5.0	1	5.0	-	-
Tendonitis	1	5.0	1	5.0	-	-
Nervous system disorders	1	5.0	1	5.0	-	-
Cerebral infarction*3	1	5.0	1	5.0	-	-
Respiratory, thoracic, and mediastinal disorders	11	55.0	1	5.0	10	50.0
Epistaxis	1	5.0	1	5.0	-	-
IPF*4,5	10	50.0	-	-	10	50.0
Pneumonia aspiration	1	5.0	1	5.0	-	-
Pneumothorax	1	5.0	1	5.0	-	-
Respiratory failure*5	1	5.0	-	-	1	5.0
Angiopathy	1	5.0	1	5.0	-	-
Air embolism	1	5.0	1	5.0	-	-

*1 Adverse events requiring any treatment or intervention
*2 Adverse events leading to study discontinuation
*3 Adverse events for which a causal relationship to Toraymyxin could not be ruled out
*4 All of the subjects died.
*5 The subjects died from respiratory failure and exacerbation of IPF.

Ten subjects (50.0%;95% CI, 27.2%-72.8%) died between the start of Toraymyxin therapy and the end of observation period (Week 12), including the subject who experienced cerebral infarction. A causal relationship of death to Toraymyxin was ruled out in all of these subjects, including the subject with cerebral infarction (Table 14).

Table 14. List of fatal cases

	No. of days after the start of Toraymyxin therapy	Cause of death	Summary of fatal case
1	55	Exacerbation of the underlying disease	The subject received Toraymyxin therapy twice, which improved acute exacerbation. Later, the subject experienced pneumonia, followed by the progression of respiratory failure, which resulted in death.
2	19	Exacerbation of the underlying disease	The subject received Toraymyxin therapy twice without improvement in the pathological condition, which resulted in death.
3	12	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times, with temporal improvement in the respiratory condition. However, the subject's condition gradually worsened, resulting in death.
4	26	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times, with temporal improvement in the respiratory condition. However, the subject's condition gradually worsened, resulting in death.
5	4	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times, with temporal improvement in the respiratory condition. However, the subject's condition gradually worsened, resulting in death.
6	41	Exacerbation of the underlying disease	The subject received Toraymyxin therapy twice without improvement in the pathological condition, which resulted in death.
7*	6	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times without improvement in the pathological condition, which resulted in death.
8	23	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times, with temporal improvement in the respiratory condition. However, the subject's condition gradually worsened, resulting in death.
9	60	Exacerbation of the underlying disease	The subject received Toraymyxin therapy 3 times, which improved the respiratory condition. Later, the subject experienced acute exacerbation again, which resulted in death.
10	7	Exacerbation of the underlying disease	The subject received Toraymyxin therapy twice without improvement in the pathological condition, which resulted in death.

* This subject experienced cerebral infarction 3 days after the start of Toraymyxin therapy.

An increased pressure at the inlet in 1 subject was reported as a malfunction, which did not lead to any adverse event.

6.A.(2) Efficacy and safety evaluation based on literature data

The literature search conducted by the applicant is outlined below. The PubMed and *Ichushi*-Web databases were searched using the following keywords for all publication years: the therapy name "PMX" and the disease names "idiopathic pulmonary fibrosis" and "acute exacerbation" (Table 15, Figure 4).

Table 15. Methodology of literature research

Database	PubMed and *Ichushi*-Web
Search keywords	PubMed (PMX OR TORAYMYXIN OR polymyxin B-immobilized OR polymyxin B-hemoperfusion OR endotoxin removal) AND (idiopathic pulmonary fibrosis OR interstitial pneumonia OR interstitial lung diseases) AND (acute exacerbation OR rapidly progressive OR acute hatred) *Ichushi*-Web (PMX OR Toraymyxin OR (Polymyxin B AND (immobilized OR hemoperfusion) OR endotoxin adsorption OR endotoxin removal) AND (idiopathic pulmonary fibrosis OR interstitial pneumonia OR interstitial lung disease) AND (acute exacerbation OR acute progression)
Filtering	• Filtered based on contents ➢ Publications from clinical studies, trials, or research, case reports, registries, meta-analyses, and systematic reviews were searched. ➢ Publications written in languages other than English or Japanese were excluded. ➢ Publications irrelevant to Toraymyxin therapy or acute exacerbation of IPF, and those that covered the same patients (duplication) were excluded. • Publication years Not filtered.

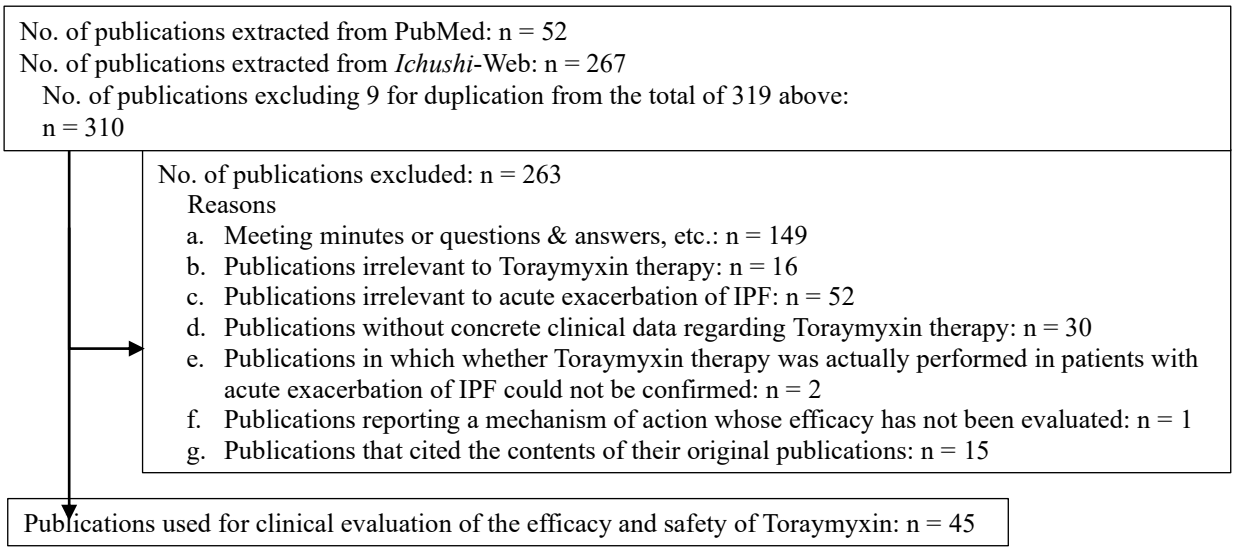

Figure 4. Flowchart of publication extraction

All of the 45 publications reported Toraymyxin therapy, consisting of 28 classified as evidence level II (cohort studies, registries, or case-control studies) and 17 classified as evidence level III (e.g., descriptive studies such as case reports, opinions from specialists, and academic meeting presentations) (publication years, 2005 to 2022). Since the number of relevant publications was limited, all of the 45 identified publications were used for clinical evaluation of Toraymyxin (Table 16).

Table 16. List of extracted publications used for clinical evaluation

No.	Author	Sample size*1	4-week survival rate (%)*2,3	12-week survival rate (%)*2,4	Oxygenation or use of mechanical ventilation*2	Adverse events*5
1	Kurahara M, *et al*.	2	-	-	One patient had an improvement in $AaDO_2$ and was weaned from the ventilator.	-
2	Seo Y *et al*.	6	66.7	-	Four of 6 patients had improvements in P/F ratio and $AaDO_2$ and were weaned from the ventilator.	-
3	Furuya S, *et al.*	1	0	0	The P/F ratio improved. The patient could not be weaned from the ventilator.	-
4	Seo N, *et al.*	6	66.7	-	The P/F ratio and $AaDO_2$ improved.	-
5	Ishimoto Y, *et al.*	2	100	50	$AaDO_2$ improved.	-
6	Fujikura S, *et al.*	2	-	-	The P/F ratio improved.	-
7	Noma S *et al*.	1	100	100	The P/F ratio improved.	-
8	Ishimoto Y, *et al.*	5	60	20	The P/F ratio and $AaDO_2$ improved.	-
9	Yoshida T, *et al.*	2	50	-	One patient had an improvement in P/F ratio. One patient had an improvement in P/F ratio temporarily, which worsened later.	-
10	Enomoto N *et al*.	3	66.7	-	The P/F ratio improved.	Platelet count decreased
11	Hashimoto S, *et al.*	3	66.7	33.3	The P/F ratio improved.	-
12	Nakayama S, *et al.*	1	-	-	The P/F ratio improved.	-
13	Miyamoto K, *et al.*	5	60	-	There was no significant difference in a change in P/F ratio between patients who were surviving at 60 days and those who were not.	No adverse event
14	Hara S *et al*.	9	55.6	33.3	The P/F ratio and $AaDO_2$ improved.	Platelet count decreased
15	Kono M *et al*.	8	-	-	The P/F ratio improved. The level of improvement did not depend on the timing of Toraymyxin therapy.	Red blood cell count decreased Platelet count decreased
16	Ikeda K, *et al.*	1	100	100	-	-
17	Watanabe T, *et al.*	3	-	-	The P/F ratio improved.	-
18	Abe S *et al*.	20	70	35	The P/F ratio and $AaDO_2$ improved.	-
19	Tachibana K, *et al*.	19	47.4	26.3	The P/F ratio improved in patients who were surviving at 30 days, but did not improve in patients who were not. The overall P/F ratio did not improve.	No adverse event
20	Abe S *et al*.	73	70.1	34.5	The P/F ratio improved.	Platelet count decreased
21	Oishi K *et al*.	9	-	66.7	The P/F ratio improved.	-
22	Tachibana K, *et al.*	1	100	100	Required amount of oxygen decreased.	-
23	Sakaguchi M, *et al.*	9	44.4	44.4	The P/F ratio improved.	-
24	Imamura R, *et al.*	9	77.8	33.3	The P/F ratio and $AaDO_2$ improved.	-
25	Takada T *et al*.	5	-	-	-	-
26	Itai J *et al*.	1	100	100	The patient had an improvement in P/F ratio and was weaned from the ventilator.	-
27	Enomoto N *et al*.	14	-	-	There was a significant difference in improvement in P/F ratio between the Toraymyxin group and the non-Toraymyxin group.	Pulmonary thromboembolism
28	Komaki C, *et al.*	5	-	-	There was a significant difference in improvement in P/F ratio between the Toraymyxin group and the non-Toraymyxin group.	No adverse event

29	Koga M, *et al.*	1	-	-	One patient had an improvement in P/F ratio and was weaned from the ventilator.	-
30	Oishi K *et al*.	27	70.4	63	There was a significant difference in improvement in P/F ratio between the Toraymyxin group and the non-Toraymyxin group.	Pulmonary thromboembolism Local haematoma
31	Ichiyasu H *et al*.	5	-	40	There was a significant difference in a change in P/F ratio between patients who were surviving at 90 days and those who were not.	-
32	Komatsu M *et al*.	3	66.7	66.7	The patients had improvements in P/F ratio and $AaDO_2$ and were weaned from the ventilator.	-
33	Baba T, *et al.*	1	-	-	-	-
34	Furusawa H *et al*.	10	-	-	The P/F ratio improved.	Haemoptysis
35	Ubukata M, *et al.*	2	-	-	The P/F ratio improved.	-
36	Yotsumoto T, *et al.*	1	0	0	The patient had no improvement in P/F ratio but was weaned from the ventilator.	Thrombosis
37	Sakamoto S *et al*.	16	-	-	-	No adverse event
38	Enomoto N *et al*.	20	-	-	-	-
39	Kim SY *et al*.	2	-	-	One patient had an improvement in P/F ratio and was weaned from the ventilator.	-
40	Ichikawa H, *et al.*	5	-	-	-	-
41	Lee JH *et al*.	9	-	-	The P/F ratio improved.	No adverse event
42	Lee SI *et al*.	2	100	0	The P/F ratio improved.	No adverse event
43	Oishi K *et al*.	30	70	60	-	Pulmonary thromboembolism Local haematoma
44	Ohashi K *et al*.	6	66.7	66.7	The P/F ratio improved.	-
45	Lee SI *et al*.	11	-	-	The P/F ratio improved.	No adverse event

*1 The number of patients with acute exacerbation of IPF who were treated with Toraymyxin
*2 Publications containing no relevant information are displayed with "-."
*3 The 4-week survival rate only in patients with acute exacerbation of IPF, including the survival rates at Days 30 and 36, and Month 1.
*4 The 12-week survival rate only in patients with acute exacerbation of IPF, including the survival rates at Day 90 and Month 3.
*5 "No adverse event" means that the publications state in their texts that no adverse event occurred. Publications containing no information about adverse events are displayed with "-."

6.A.(2).1) Efficacy evaluation

In the above literature references, the weighted means (weighted by the number of patients) of 4- and 12-week survival rates were 66.6% and 43.3%, respectively in patients with acute exacerbation of IPF treated with Toraymyxin. These results are similar to the 4-week survival rate (65.0%) and 12-week survival rate (50.0%) in the Advanced Medicine Care B Study. Two literature references (Nos. 27 and 30) included only patients with acute exacerbation of IPF and compared the results between the Toraymyxin group and the non-Toraymyxin group. The 12-month survival rate in Literature Reference No. 27 was higher in the Toraymyxin group (14 patients) than in the non-Toraymyxin group (17 patients) (48.2% vs. 5.9%). The 30-day, 90-day, and 12-month survival rates in Literature Reference No. 30 were all higher in the Toraymyxin group (27 patients) than in the non-Toraymyxin group (23 patients) (70.4% vs. 47.9%, 63.0% vs. 26.1%, and 41.7% vs. 9.8%, respectively). In both references, the survival rates were higher in the Toraymyxin group than in the non-Toraymyxin group.

A total of 37 of the 45 references reported improvement in oxygenation indexes, including the P/F ratio and $AaDO_2$, and weaning from ventilator, as demonstrated by the comparison between before and after Toraymyxin therapy or between the Toraymyxin group and the non-Toraymyxin group; this suggested the contribution of Toraymyxin therapy to improvement in oxygenation.

6.A.(2).2) Safety evaluation

Of the 45 references, 9 reported the following adverse events: Platelet count decreased in 4 references (Nos. 10, 14, 15, and 20), pulmonary thromboembolism in 3 references (Nos. 27, 30, and 43), local haematoma in 2 references (Nos. 30 and 43), red blood cell count decreased in 1 reference (No. 15), haemoptysis in 1 reference (No. 34), and thrombosis in 1 reference (No. 36).

None of the events of platelet count decreased were considered significant because the decreased platelet counts in the patients after Toraymyxin therapy were not classified as Grade ≥3 of Common Terminology Criteria for Adverse Events (CTCAE). None of the events of pulmonary thromboembolism were considered significant because all were reported as "mild in severity" and resolved after anticoagulant therapy. Other adverse events (local haematoma, red blood cell count decreased, haemoptysis, and thrombosis) were not particularly concerning because they occurred only in a small number of patients and were mild in severity or not reported as serious.

No literature reference reported any malfunction.

6.B Outline of the review conducted by PMDA

PMDA reviewed the submitted data with focus on the following issues.

6.B.(1) Use of the clinical evaluation report for efficacy and safety evaluation

In principle, the add-on effect of Toraymyxin therapy to conventional therapy in patients using Toraymyxin for the proposed expanded indication, should be verified in a control study designed based on the findings from the Advanced Medical Care B Study. For the reasons presented below, however, it is acceptable to evaluate the efficacy and safety of Toraymyxin based on the clinical evaluation report summarizing the data from the Advanced Medical Care B Study and the relevant publications, provided that the conditional approval system for medical devices is applied to the present partial change application.

- Toraymyxin has been widely used in clinical practice since its initial approval in 1993, without any significant safety problem. Since the present partial change application includes no change in the design of Toraymyxin, there would be no significant device- or procedure-related safety concerns, other than those that might be associated with the proposed expanded indication.
- The Advanced Medical Care B Study was conducted according to a detailed protocol that defined the inclusion and exclusion criteria, as well as conditions of preoperative and postoperative examinations, and pharmacotherapy. The primary efficacy endpoint was the survival rate. For safety assessment, adverse events can be evaluated based on the individual case data collected in this study. The post-marketing efficacy and safety of Toraymyxin can be estimated to some extent based on the results of the study, although they are exploratory.
- The Advanced Medical Care B Study was conducted in compliance with the Declaration of Helsinki and the "Ethics Guidelines for Clinical Research" to ensure that ethical considerations were taken into account. In addition, the applicant has taken necessary measures for data assurance, including source document verification and auditing.

- Probably 7 to 8 years will be required to complete a new clinical study of a similar sample size to that of the Advanced Medical Care B Study. As the Japanese Respiratory Society has submitted a written request for early regulatory approval of Toraymyxin for the expanded indication, there is a high clinical need for Toraymyxin. For these reasons, the early introduction of Toraymyxin into Japan based on the currently available data (including the results of the Advanced Medical Care B Study) using the conditional approval system appears to be useful, provided that sufficient safety measures are installed. This is because Toraymyxin offers a new treatment option for acute exacerbation of IPF, which has poor prognosis and has no effective therapy other than pharmacotherapy.

6.B.(2) Advanced Medical Care B Study

6.B.(2).1) Appropriateness of external reference values

The applicant's explanation about the appropriateness of the external reference value (i.e., the upper limit of 4-week survival rate of 40% for the conventional therapy) used in the Advanced Medical Care B Study:

During the planning stage of the Advanced Medical Care B Study, the external reference value was defined as 40% based on the 4-week survival rates reported in the literature references.[11,14] In preparation for the present partial change application, a comprehensive publication search was conducted to examine the appropriateness of the external reference value; the search showed that the maximum 4-week survival rate was 42%. Further, the mean 4-week survival rate in patients with acute exacerbation of IPF in recent years (2014-2019) was 33.9% according to the patient information registered in the medical practice database of [redacted]. Both of these 4-week survival rates, calculated based on data from publications (which were appropriate for comparison) and the database of [redacted], were lower or almost equal to 40%. Therefore, the external reference value of 40% used in the Advanced Medical Care B Study was appropriate.

A recent publication regarding pharmacotherapy[15] reports that 4-week survival rate in patients with acute exacerbation of IPF has been improving, but "the 4-week survival rate of 40%" was a reasonable value at the time of the study. The external reference value used in the Advanced Medical Care B Study was therefore acceptable.

6.B.(2).2) Justification for conventional pharmacotherapy administered in Advanced Medical Care B Study

The protocol of the Advanced Medical Care B Study defined specific drugs and their dosing regimens to be used as the conventional pharmacotherapy (i.e., the combination of steroid pulse therapy, neutrophil elastase inhibitor therapy, and immunosuppressant therapy). The enrolled subjects began to receive the pharmacotherapy according to the protocol before the start of Toraymyxin therapy. PMDA asked the applicant to explain whether the details of the pharmacotherapy were appropriate.

The applicant's explanation:

The details of the pharmacotherapy specified in the protocol of the Advanced Medical Care B Study were reviewed by respiratory specialists at the study sites with reference to the "Diagnosis and

Treatment Guidance of Idiopathic Interstitial Pneumonia (Second Edition) (in Japanese).”[16] At the beginning of its pharmacotherapy section, the guidance states that “there is no established pharmacotherapy with known effectiveness for acute exacerbation of IPF.” The guidance also includes the phrase “typically 1,000 mg/day as the starting dose” for steroid pulse therapy, only providing some information but not a specific starting dose. As indicated by this expression, medical institutions currently treat acute exacerbation of IPF through trial and error, providing patients with pharmacotherapy or other various therapies according to their pathological conditions, etc.

For the conduct of the clinical research “Advanced Medical Care B Study,” there needed to be a certain level of standardization of the treatment of acute exacerbation of IPF in order to equalize baseline treatment characteristics. The details of the pharmacotherapy were specified in the protocol of the study, taking into consideration the clinical practice standards used at both study sites. This means that the details were determined according to the above guidance. However, since the guidance included no clear information about doses for steroid pulse therapy, the starting dose of steroid pulse therapy was defined as 500 mg/day according to the clinical practice standards used at the study sites.

PMDA’s view:
On the basis of the information in the guidelines and the comments from the Expert Discussion, the conventional pharmacotherapy administered in the study was appropriate. The protocol specified the particular types of steroids, neutrophil elastase inhibitors, and immunosuppressants, and their dosing regimens for the conventional pharmacotherapy; this was appropriate. Further, a publication reported patients who received corticosteroid therapy at 500 mg/day as the starting dose.[17] PMDA therefore concluded that the applicant’s explanation was acceptable.

6.B.(3) Efficacy and safety of Toraymyxin

6.B.(3).1) Efficacy

The results of the Advanced Medical Care B Study, although exploratory, showed a 4-week survival rate exceeding the outcomes of the conventional pharmacotherapy, with improvement in oxygenation and chest X-ray findings. The other literature references also reported similar outcomes to those in the Advanced Medical Care B Study. PMDA concluded that Toraymyxin was shown to have efficacy to some extent.

6.B.(3).2) Safety

In the Advanced Medical Care B Study, cerebral infarction occurred in 1 subject. The event was reported as a serious adverse event, for which a causal relationship to Toraymyxin could not be ruled out. It was judged that the cerebral infarction might have been due to procedural air embolism, but this case could have been cerebral infarction associated with worsened general condition due to acute exacerbation of IPF, because the subject had complications (hypertension, etc.) that increase the risk of cerebral infarction. Since cerebral infarction has been reported only in 1 subject to date, (a) relevant information should be provided through the Information on Precautions, etc., (b) the occurrence of this event should be investigated according to the medical device risk management plan, described later in Section 7, and (c) additional actions should be taken as necessary. The other serious adverse events were unrelated to Toraymyxin. The adverse events for which a causal relationship to Toraymyxin

could not be ruled out, also had favorable outcomes. The literature references revealed no special safety concerns about Toraymyxin. PMDA concluded that the clinical safety profile of Toraymyxin was acceptable for the proposed expanded indication.

On the basis of 6.B.(3).1) and 6.B.(3).2) above, PMDA considers that the clinical evaluation, although exploratory, has suggested the efficacy and safety of Toraymyxin in patients with acute exacerbation of IPF. Patients eligible for Toraymyxin therapy have severe conditions with no effective therapy available, other than pharmacotherapy. When those patients do not respond to pharmacotherapy, their prognosis becomes poor in a relatively short period of time. There is, therefore, a high clinical need for a new treatment option for acute exacerbation of IPF. Taking into consideration the comments from the Expert Discussion, PMDA have concluded that although currently there is only limited evidence on Toraymyxin therapy for the proposed expanded indication, Toraymyxin is expected to be useful, provided that sufficient post-marketing safety measures, described later in Section 7, are installed to ensure a favorable risk-benefit balance of Toraymyxin for this indication.

6.B.(4) Eligible patients and intended use

6.B.(4).1) Eligible patients

The applicant's explanation:

For the reasons described below, patients with triggered acute exacerbation of IPF and those with a P/F ratio of ≥300 (i.e., populations excluded from the Advanced Medical Care B Study) should be made eligible for the proposed expanded indication.

Since the International Working Group Report[18] was published in 2016 after the start of the Advanced Medical Care B Study, patients with triggered acute exacerbation of IPF have also been diagnosed with acute exacerbation of IPF. Later research reported that there was no difference in the pathology, treatment, or prognosis between patients with triggered and idiopathic acute exacerbation of IPF.[19,20] Okuda et al. also reported that Toraymyxin therapy resulted in no significant difference in prognosis between patients with triggered acute exacerbation (n =10) and those with idiopathic acute exacerbation (n = 29).[21] Even before the publication of the above report, there were reports that Toraymyxin had efficacy in treating patients who experienced acute exacerbation triggered by infection.[22,23,24] Since antimicrobials have been administered empirically as part of treatment of acute exacerbation of IPF, a certain number of cases diagnosed as idiopathic acute exacerbation (i.e., acute exacerbation considered to have no triggers) of IPF according to the existing diagnostic criteria, might have been actually triggered by infection, etc. The known causative agents for acute exacerbation of IPF include endotoxin, white blood cells, and cytokines, although no mechanism of acute exacerbation has been identified. Several reports have suggested Toraymyxin removed not only endotoxin but also these causative agents.[25,26,27] In principle, therefore, Toraymyxin is expected to have efficacy also in patients with acute exacerbation of IPF triggered by infection or other factors as in those with idiopathic acute exacerbation. To date, Toraymyxin has been used in approximately [redacted] patients since its initial approval in 1993 for the approved indication. In clinical practice, Toraymyxin has reportedly been used in the treatment of not only gram-negative infection but also serious infections with gram-positive bacteria,[28] influenza virus,[29,30,31] COVID-19,[32,33] etc. The post-marketing safety information including cases of these infections treated with Toraymyxin shows that the incidence of

malfunctions or adverse events associated with “worsened infection” or “white blood cell decreased” was extremely low: only 0.0015% ([redacted] patients). In summary, the treatment mechanism of Toraymyxin and findings regarding Toraymyxin suggest that patients with acute exacerbation of IPF triggered by infection or other causes are expected to obtain the same therapeutic efficacy of Toraymyxin that has been observed in idiopathic acute exacerbation of IPF, although the mechanism of acute exacerbation of IPF remains unclear. Even if Toraymyxin is used in patients with triggered acute exacerbation of IPF, it is unlikely to cause adverse events that may lead to aggravation of infection.

Toraymyxin has reportedly been used in patients with a P/F ratio of ≥300.[11,34] However, this patient population was excluded from the Advanced Medical Care B Study to ensure that only patients with respiratory failure meeting objective criteria are enrolled. Toraymyxin therapy has been prescribed to relatively severe patients, as demonstrated by the P/F ratios in the subjects enrolled in the Advanced Medical Care B Study and in patients with acute exacerbation of IPF treated with Toraymyxin reported by the publications. Therefore, “a P/F ratio of <300” can be used as a patient eligibility criterion for Toraymyxin therapy. However, the P/F ratio changes with every moment according to treatment situation and does not reflect arterial partial pressure of carbon dioxide ($PaCO_2$) levels. Further, the P/F ratio may underestimate the severity of respiratory difficulty. Since acute exacerbation of IPF is a rare disease with no therapy available other than pharmacotherapy, healthcare professionals in clinical practice have expressed a strong need for the use of Toraymyxin in patients with a P/F ratio of ≥300. Thus patients with a P/F ratio of ≥300, the population excluded from the Advanced Medical Care B Study, should be made eligible for the expanded indication.

PMDA’s view in view of the comments from the Expert Discussion:
PMDA accepts the applicant’s explanation that there is no substantial efficacy or safety concern about using Toraymyxin in patients with triggered acute exacerbation of IPF and those with a P/F ratio of ≥300. For the reasons shown below, and considering the seriousness of the disease and the high need of Toraymyxin, it is acceptable to make these patients eligible for the expanded indication, provided that the medical device risk management plan is prepared as described later in Section 7.

- The current treatment strategy is the same for patients with triggered acute exacerbation and those with idiopathic acute exacerbation, and there is reportedly no difference in treatment outcomes between these patient groups, including those treated with Toraymyxin. Toraymyxin is associated with a low incidence of aggravated infection in the approved indication. The mechanism of action of Toraymyxin also suggests that it has a low risk of aggravating infection in patients with triggered acute exacerbation of IPF.
- Toraymyxin may be used in patients with milder disease than those enrolled in the Advanced Medical Care B Study. Since the P/F ratio may change acutely in patients with acute exacerbation of IPF, patients with a P/F ratio of ≥300 who do not respond to conventional therapy are also expected to benefit from Toraymyxin therapy. In addition, some small-scale research has shown no substantial safety concerns about Toraymyxin. There appears to be no concerns about an increased risk for using Toraymyxin in this patient population compared with the risk seen in the Advanced Medical Care B Study.

6.B.(4).2) Intended use or indication

The Advanced Medical Care B Study suggested the efficacy and safety of Toraymyxin in patients who had severe oxygenation impairment (mean P/F of 198.1) even after pharmacotherapy. Pharmacotherapy is the standard treatment for acute exacerbation of IPF and the invasiveness and evidence of Toraymyxin therapy are limited. Therefore, its clinical positioning should be a new treatment option that may improve the prognosis and respiratory condition of patients who have not responded to pharmacotherapy. On the basis of these discussions, PMDA concluded that the "intended use or indication" of Toraymyxin should be as shown below. The definition of acute exacerbation of IPF should not be specified in the intended use of Toraymyxin but instead should be specified in the proper use standards to be prepared by with related academic society. This is because the guidelines, etc. may be revised as evidence is accumulated in the future, and because the patient eligibility criteria for Toraymyxin therapy may be modified based on the results of the use-results survey of Toraymyxin.

Intended use or indication (The underlined parts were proposed in the present partial change application.)

Toraymyxin is intended to improve the pathological condition of the following patients:

(1) Toraymyxin is intended to improve the pathological condition of patients with a severe pathological condition associated with endotoxemia or suspected gram-negative infection.
A severe pathological condition should typically meet at least 2 of the following criteria:
- Body temperature of >38˚C or <36˚C
- Heart rate of >90 beats/min
- Respiratory rate of >20 breaths/min or $PaCO_2$ of <4.3 kPa (32 torr)
- White blood cell count of >12000 cells/mm^3 or <4000 cells/mm^3, or ≥10% stab neutrophils

(2) <u>Patients with acute exacerbation of idiopathic pulmonary fibrosis who have not responded to conventional therapy</u>

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant submitted a medical device risk management plan (draft) with the present partial change application using the conditional approval system (Table 17). Table 18 presents a use-results survey plan (draft) to be conducted as part of the medical device risk management plan.

Table 17. Summary of the medical device risk management plan (draft)

Summary of the medical device risk management plan	
Safety specifications	Important identified risks: Increased pressure at the inlet
	Important potential risks: 1. Platelet count decreased 2. Allergy, shock, anaphylactic shock 3. Cerebral infarction 4. Thrombosis, embolism
	Important missing information*: Patients with IPF trigger
Efficacy specifications	• Survival rate at Week 4 after acute exacerbation of IPF • Survival rate at Week 12 after acute exacerbation of IPF (in comparison with patients untreated with Toraymyxin) • The change in oxygenation (P/F ratio and $AaDO_2$) before and after Toraymyxin therapy • Improvement in chest image findings (X-ray or HRCT) • The change in blood LDH before and after Toraymyxin therapy • The change in blood CRP before and after Toraymyxin therapy • Duration of mechanical ventilation • The change in KL-6, SP-D, ferritin, and D-dimer before and after Toraymyxin therapy • Comparison of efficacy between patients with triggered and idiopathic acute exacerbation of IPF
Summary of medical device pharmacovigilance plan	
Routine medical device pharmacovigilance activities	Collection, confirmation, and analysis of safety management information including spontaneous reports, publications/information at academic meetings, and foreign corrective action reports. Discussion on necessary safety measures and execution of safety assurance measures based on the results of the above analysis.
Additional medical device pharmacovigilance activities	Use-results survey
Summary of the plans for efficacy survey and studies	
	Use-results survey
Summary of the risk minimization plan	
Routine risk minimization activities	Provision of information and precautions through the Information on Precautions, etc.

Additional risk minimization activities	Proper use management activities **Key items of the proper use standards** <u>Patient eligibility criteria</u> Patients with acute exacerbation of IPF who meet both of the following criteria are eligible for Toraymyxin therapy. Data from these patients will be registered and analyzed in the use-results survey. 1. Patients with a P/F ratio of <300 before the start of Toraymyxin therapy 2. Patients who require Toraymyxin therapy in addition to conventional therapy (e.g., pharmacotherapy including steroid pulse therapy). *Diagnostic criteria for acute exacerbation of IPF* Acute exacerbation of IPF is diagnosed when all of the following conditions are observed within the past 1 month in the course of IPF: (a). Increased dyspnea (b). A honeycomb lung(s) + new ground-glass opacity/infiltrative shadows on HRCT (c). Decreased PaO_2 (PaO_2 ≥10 mmHg under the same conditions) <u>Survey system</u> To execute the treatment of acute exacerbation of IPF with Toraymyxin, collaboration among healthcare professionals with specialized knowledge and experience in different medical fields, including disease diagnosis, selection of therapy, and extracorporeal circulation, is essential. Each survey site participating in the use-results survey must meet both of the following criteria: 1. Physicians who select patients eligible for Toraymyxin therapy must be specialists accredited by the Japanese Respiratory Society or must have sufficient specialized knowledge about IPF and acute exacerbation of IPF, and must have knowledge and experience in hemoperfusion therapy. 2. In Toraymyxin therapy, not only physicians who select eligible patients but also healthcare professionals from multiple departments, including physicians and clinical technicians with sufficient knowledge and experience in hemoperfusion therapy, must collaborate together. <u>Survey sites</u> To participate in the use-results survey, medical institutions must understand the concept of the conditional approval system and consent to register necessary data for the use-results survey in a timely manner. They must also meet all of the following criteria for survey sites and be accredited by the data review committee consisting of members of the Japanese Respiratory Society. *Survey site criteria* Medical institutions are eligible if they: 1. Have a respiratory medicine department that provides healthcare services covered by public health insurance. 2. Have at least 1 full-time specialist accredited by the Japanese Respiratory Society. 3. Treat at least 20 patients with IPF per year. 4. Have at least 1 full-time clinical technician specialized in hemoperfusion therapy. 5. Have a multipurpose blood treatment equipment, etc. for hemoperfusion therapy that is maintained and managed appropriately. 6. Have a treatment system that is capable of dealing with events (e.g., decreased blood pressure) commonly associated with hemoperfusion therapy. 7. Perform hemoperfusion therapy in ≥10 patients per year.

* Missing information for predicting the post-marketing safety of a medical device, etc. because there is no sufficient information available at the stage of preparing the medical device risk management plan.

Table 18. Summary of the use-results survey plan (draft)

Item	Description
Population	All patients who are treated with Toraymyxin for acute exacerbation of IPF, which is the proposed intended use or indication. Patients can be enrolled as comparators (i.e., patients untreated with Toraymyxin) if they have experienced acute exacerbation of IPF between the market launch of nintedanib ethanesulfonate in Japan and the approval of the present partial change application. For every 1 patient to be treated with Toraymyxin, 3 comparators will be enrolled in the order of onset date of acute exacerbation (from oldest to newest) after approval of the present partial change application.
Target sample size	The target sample size up to Stage 3 is 190. Patients can be enrolled as comparators if they have received treatment for acute exacerbation of IPF at the survey sites before approval of the present partial change application. The target number of comparators is 570.
Rationale for the sample size	The sample size of 190 was determined assuming the 4-week survival rate of 70% and 55%, respectively, for patients treated and untreated with Toraymyxin, in view of dropouts, etc.
Planned number of survey sites	Medical institutions must meet the proper use standards prepared by the Japanese Respiratory Society.
Observation period	12 weeks
Overall survey period	6 years (enrollment, 4.5 years; observation, 12 weeks; survey form collection, 6 months; survey data finalization, analysis, preparation for application, 9 months)
Key items to be surveyed	Safety: Increased pressure at the inlet, platelet count decreased, allergy, shock, anaphylactic shock, cerebral infarction, thrombosis, embolism, triggered acute exacerbation of IPF, efficacy specifications in the medical device risk management plan (primary and secondary efficacy endpoints of the survey), and death
Key items to be analyzed	(1) Safety Incidences of malfunctions and adverse events (overall and each key survey item) (2) Efficacy *Primary endpoint* • Survival rate at Week 4 after acute exacerbation of IPF *Secondary efficacy endpoints* • Survival rate at Week 12 after acute exacerbation of IPF (versus patients untreated with Toraymyxin) • The change in oxygenation (P/F ratio and $AaDO_2$) before and after Toraymyxin therapy • Improvement in chest images (X-ray or HRCT) • The change in blood LDH before and after Toraymyxin therapy • The change in blood CRP before and after Toraymyxin therapy • Duration of mechanical ventilation • The change in KL-6, SP-D, ferritin, and D-dimer before and after Toraymyxin therapy • Comparison of efficacy between patients with triggered and idiopathic acute exacerbation of IPF
Additional actions that may be taken in response to survey results and criteria that trigger actions	• Revision of the Information on Precautions, etc. should be considered when: ➢ An important unknown malfunction is suggested; ➢ The incidence of malfunctions increases substantially; ➢ Some safety or efficacy issue are identified; or ➢ A different type of malfunction is suggested. • The necessity of modifying the survey plan, including new safety specifications, should be considered. • When a new safety specification is added, the necessity of risk minimization activities related to this addition should be discussed.

Timing to evaluate the progress and results of the survey, or to report them to PMDA, and its rationale	• At transition to Stage 2. The efficacy and safety will be evaluated in the first 20 patients treated with Toraymyxin in Stage 1. • At transition to Stage 3. The efficacy and safety will be evaluated in ≥110 patients treated with Toraymyxin. • Annual periodic reporting. Safety information about malfunctions, etc. will be reviewed comprehensively. • At evaluation of use results.
Others	**Revision of the plan** The progress of the survey, number of dropouts, unknown or serious malfunctions, a substantial increase in the incidence of specific malfunctions, the appropriateness of survey items, etc. will be constantly investigated during the survey. The survey plan will be reviewed and revised if necessary. When a partial change application for the intended use or indication is approved during the survey, revision of the survey plan will also be considered. The survey plan will be revised if necessary.
	Safety and efficacy evaluation in cooperation with the Diffuse Lung Disease Assembly of the Japanese Respiratory Society • In order to ensure the safety of Toraymyxin and take risk management measures appropriately based on the use results, the numbers of survey sites and patients will be increased step by step. ➢ In Stage 1, Toraymyxin will be introduced to approximately 8 survey sites to treat patients with acute exacerbation of IPF with a P/F ratio of <300. If the 4-week survival rate in the first 20 patients is ≥40%, the efficacy is considered to be acceptable. If there is no significant safety concern as confirmed by the data review committee, the survey will proceed to Stage 2. ➢ In Stage 2, the survey will enroll approximately 16 sites. The efficacy will be evaluated by comparing the 4-week survival rate between ≥110 patients treated with Toraymyxin and those untreated with Toraymyxin using a propensity score. If there is no significant safety concern as confirmed by the data review committee, the survey will proceed to Stage 3. ➢ In Stage 3, patients with acute exacerbation of IPF with a P/F ratio of ≥300 will be allowed to receive Toraymyxin therapy. The efficacy of treatment will be evaluated by comparing the 4-week survival rate between the patients treated with Toraymyxin and those untreated with Toraymyxin using a propensity score. • If the criteria for proceeding to a next stage are not met, the use-results survey plan, medical device risk management plan, and proper use standards will be reviewed after consultation with the Diffuse Lung Disease Assembly of the Japanese Respiratory Society and PMDA. • The marketing authorization holder will collect data on malfunctions and adverse events experienced by patients treated with Toraymyxin every 6 months and report the data to the review committee. The marketing authorization holder will provide the data review committee with the efficacy and safety data available at submission of annual periodic reports and at application of the use-results evaluation. • After consultation with the Diffuse Lung Disease Assembly of the Japanese Respiratory Society and PMDA, the final decision will be made regarding whether to continue Toraymyxin therapy, eligible patients, whether to revise the proper use standards, whether to increase the number of survey sites, and the necessity of additional safety measures.

As described earlier in Section "6.B.(3) Efficacy and safety of Toraymyxin," only limited data are available regarding the clinical efficacy and safety of Toraymyxin used to treat acute exacerbation of IPF, the expanded indication proposed in the present partial change application. Physicians who diagnose and treat sepsis, the approved indication of Toraymyxin, are different from those who diagnose and treat acute exacerbation of IPF. The key issues of the medical device risk management plan required for the safe and effective introduction of Toraymyxin to clinical practice to treat acute exacerbation of IPF are as follows: (1) Establishment of eligibility criteria for physicians and medical institutions that perform Toraymyxin therapy, and training of healthcare professionals; (2) risk

management using the results of the post-marketing use-results survey; and (3) a stepwise expansion of eligible patients and medical institutions.

The applicant's explanation about each key issue:

7.A.(1) Eligibility criteria for physicians and medical institutions, and training for healthcare professionals

Performing Toraymyxin therapy for the proposed expanded indication requires collaboration among healthcare professionals with specialized knowledge and experience in different medical fields, including disease diagnosis, selection of conventional therapy, and extracorporeal circulation. Therefore, the proper use standards prepared by the Japanese Respiratory Society require that medical institutions participating in the use-results survey have an established system that meets all of the following criteria:

- Physicians who select patients eligible for Toraymyxin therapy must be specialists accredited by the Japanese Respiratory Society or must have sufficient specialized knowledge about IPF and acute exacerbation of IPF, and must have knowledge and experience in hemoperfusion therapy.
- In Toraymyxin therapy, not only physicians who select eligible patients but also healthcare professionals from multiple departments, including physicians and clinical technicians with sufficient knowledge and experience in hemoperfusion therapy, must collaborate together.

There are some differences between Toraymyxin therapy for the proposed expanded indication and that for the approved indication (e.g., the proposed indication requires a longer use of Toraymyxin). For the reasons shown below, however, neither classroom lecture nor hands-on training regarding the proposed expanded indication need not be provided to healthcare professionals. Providing healthcare professionals with Information on Precautions, etc. and materials summarizing patient eligibility criteria, disease-specific considerations, and other relevant information, will be sufficient for them to understand the differences.

- Toraymyxin has long been used in clinical practice since the initial approval for the treatment of sepsis in 1993. The directions for use for the approved indication are well known.
- The proper use standards specify that not only physicians who select eligible patients but also healthcare professionals from multiple departments, including physicians and clinical technicians with sufficient knowledge and experience in hemoperfusion therapy, must collaborate together in the treatment of acute exacerbation of IPF with Toraymyxin.

7.A.(2) Risk management using the results of the use-results survey

Using the results of the use-results survey (Table 18), the data review committee will monitor data for proper risk analysis. The applicant will analyze data on malfunctions and adverse events experienced by patients treated with Toraymyxin for the proposed expanded indication once a year and report the results to the data review committee and PMDA. Whether to continue Toraymyxin therapy, whether to revise the proper use standards, and the necessity of additional safety measures will be discussed with the Japanese Respiratory Society and PMDA. Each revision of the written information material for patients will be reported to the data review committee.

7.A.(3) Stepwise expansion of eligible patients and survey sites

In order to ensure the efficacy and safety of Toraymyxin and take the risk management measures appropriately based on the use results, the number of survey sites and eligible patients will be increased step by step. In Stage 1, Toraymyxin will be used only in a small number of survey sites to treat patients with acute exacerbation of IPF with a P/F ratio of <300. If no significant efficacy or safety concerns have been identified in the first 20 patients enrolled at the sites and expanding the number of survey sites deems appropriate, the survey will proceed to Stage 2. If the data review committee judges that no significant efficacy or safety concerns have been identified in Stages 1 and 2, the survey will proceed to Stage 3 to include patients with a P/F ratio of ≥300. Whether to expand eligible patients and survey sites will be discussed with the Japanese Respiratory Society and PMDA as described in Section "7.A.(2) Risk management using the results of the use-results survey."

7.B Outline of the review conducted by PMDA

Toraymyxin, whose efficacy and safety was evaluated based on the limited clinical data, is Japan's first medical device indicated for direct hemoperfusion to treat acute exacerbation of IPF. The application was submitted under the conditional approval system. Prior to the introduction of Toraymyxin for the proposed expanded indication, a sufficient risk management system should be established. Further, the applicant should (a) collect efficacy and safety data regarding Toraymyxin used for the proposed expanded indication, (b) analyze the collected data and share analysis results with the Japanese Respiratory Society and PMDA in a timely manner, and (c) take additional risk reduction measures promptly as necessary. These activities are essential to ensure the efficacy and safety of Toraymyxin therapy.

On the basis of the discussions below, PMDA concluded that the medical device risk management plan proposed by the applicant was adequate because it plans to ensure the efficacy and safety of Toraymyxin by following the proper use standards prepared by with related academic society and conducting a use-results survey.

Eligibility criteria for physicians and medical institutions, and training for healthcare professionals

Acute exacerbation of IPF, for which Toraymyxin will be indicated, is a pathological condition due to acute disease progression during the chronic course of IPF. This disease should be carefully differentiated from other infectious diseases such as pneumonia. Therefore physicians with sufficient experience in diagnosis and treatment of respiratory diseases including IPF and healthcare professionals well-versed in hemoperfusion therapy, should be involved in Toraymyxin therapy. The eligibility criteria for medical institutions and physicians/technicians prepared by with related academic society are appropriate because they meet these requirements.

PMDA agreed on the following applicant's policy on training:

Hands-on training for Toraymyxin is unnecessary because there is no procedural difference between in Toraymyxin therapy between the proposed expanded indication and the approved indication, other than that the former requires a longer use of Toraymyxin, and because this treatment will be performed only at medical institutions with experience in hemoperfusion therapy including Toraymyxin. The

Information on Precautions, etc. and other materials will be provided to healthcare professionals to help them understand the considerations related to Toraymyxin therapy.

Risk management using the results of the use-results survey

Since only limited data are available regarding the clinical efficacy and safety of Toraymyxin used to treat acute exacerbation of IPF, the results of the use-results survey of Toraymyxin should be analyzed in a timely manner and take additional measures as necessary. The submitted draft use-results survey plan is appropriate because it uses (a) the endpoints determined from the results of the Advanced Medical Care B Study and because the prognostic factors of IPF[3] and (b) the observation period determined based on the standard survival period (≤2 months[1]) of patients with acute exacerbation of IPF. For the following reasons, PMDA accepts the proposed analysis methodology that will compare treatment outcomes before and after the approval of Toraymyxin within each survey site and the rationale for the sample size:

- Once introduced to Japan, Toraymyxin will be preferentially used for the treatment of acute exacerbation of IPF. The baseline characteristics of patients untreated with Toraymyxin may differ between before and after the introduction of Toraymyxin.
- There is no fully evidence-based therapy for acute exacerbation of IPF. The patient's baseline characteristics may differ between survey sites because the sites may have a different protocol for conventional therapy of acute exacerbation of IPF.
- Data from patients untreated with Toraymyxin will be collected only after the approval of "Ofev Capsules 100 mg" and "Ofev Capsules 150 mg," drugs used to treat IPF, to reflect the latest clinical practice of the treatment of acute exacerbation of IPF.

Stepwise expansion of eligible patients and survey sites

As described earlier in Section "6.B.(4).1) Eligible patients," Toraymyxin will also be indicated, in the post-marketing setting, for patients having baseline characteristics that were excluded from the Advanced Medical Care B Study. Since the Advanced Medical Care B Study provided only limited data, the efficacy and safety of Toraymyxin should be evaluated in patients who are as severe as the subjects of this study to ensure the post-marketing efficacy and safety of Toraymyxin. PMDA instructed the applicant to assess use results in a step-by-step manner and expand patient eligibility after consultation with the Japanese Respiratory Society and PMDA. The applicant agreed.

In accordance with the submitted draft use-results survey plan (Table 18), Stages 1 and 2 of the survey will enroll patients with a P/F ratio of <300, as in the Advanced Medical Care B Study. After the efficacy and safety of Toraymyxin in these patients is statistically analyzed, Stage 3 will include patients with a P/F ratio of ≥300. PMDA concluded that this strategy for survey scale-up was acceptable.

On the basis of the above discussions and the comments from the Expert Discussion, PMDA concluded that the medical device risk management plan (draft) proposed by the applicant was adequate and should be imposed as Approval Condition 1. The eligibility criteria for physicians and medical institutions, and requirements for information provision to healthcare professionals should be imposed as Approval Condition 2. The conduct of the use-results survey should be imposed as

Approval Condition 3. The medical device risk management plan should be reviewed as necessary based on post-marketing use results with Toraymyxin.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The present partial change approval has proposed an additional indication (acute exacerbation of IPF) of Toraymyxin using the conditional approval system. In the review of Toraymyxin, PMDA's review primarily focused on (1) the efficacy and safety of Toraymyxin, (2) eligible patients, and (3) medical device risk management plan. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion:

(1) Efficacy and safety of Toraymyxin

In the Advanced Medical Care B Study of Toraymyxin, the 4-week survival rate exceeded the outcomes of the conventional therapy with improvement in oxygenation and chest X-ray findings, without any significant safety concerns. Since these results are consistent with those reported in the other literature references, they suggest the efficacy and safety of Toraymyxin in patients with acute exacerbation of IPF, although they are exploratory data. There is a high clinical need for a new therapy for acute exacerbation of IPF because pharmacotherapy is the only treatment option available for patients with this severe condition, the target population of Toraymyxin, and because their prognosis is poor if they do not respond to pharmacotherapy. Although currently there is only limited clinical data, the risk-benefit balance of Toraymyxin can be maintained by implementing sufficient post-marketing safety measures. PMDA concluded that Toraymyxin could be a useful therapy for patients who do not respond to conventional therapy.

(2) Survey population

The risk-benefit balance of Toraymyxin does not appear to differ significantly between the subjects of Advanced Medical Care B Study and patients with triggered acute exacerbation of IPF or with a P/F ratio of ≥300 (i.e., patients excluded from the study). Making these patients eligible for the expanded indication is acceptable considering (a) the seriousness of the disease and the high need of Toraymyxin, and (b) the concept of the conditional approval system, provided that the efficacy and safety (risk-benefit balance) of Toraymyxin are fully evaluated in the post-marketing setting according to the medical device risk management plan. However, the inclusion of patients with a P/F ratio of ≥300 from the early stage of marketing of Toraymyxin may influence the results of the use-results survey. Therefore the survey should first enroll patients who were as severe as subjects of the Advanced

Medical Care B Study and then should include patients with a P/F ratio of ≥300 in a step-by-step manner after confirmation of post-marketing use results.

(3) Medical device risk management plan

Toraymyxin is Japan's first medical device indicated for direct hemoperfusion to treat acute exacerbation of IPF. The present application was submitted under the conditional approval system. Prior to the introduction of Toraymyxin, the applicant should establish an adequate risk management system. Further, the applicant should (a) analyze the efficacy and safety data of Toraymyxin, (b) share the analysis results with the Japanese Respiratory Society and PMDA in a timely manner, and (c) take additional risk mitigation measures promptly as necessary. Since these activities are essential to ensure the efficacy and safety of Toraymyxin therapy, they should be imposed as Approval Condition 1.

To ensure the effective and safe introduction of Toraymyxin, physicians with adequate experience in the diagnosis and treatment of patients with acute exacerbation of IPF should select eligible patients for Toraymyxin therapy and treat them at medical institutions with adequate experience in hemoperfusion therapy (including Toraymyxin) and a well-established medical care system for the treatment of IPF. Compliance with the proper use standards prepared by with related academic society is also important and should be imposed as Approval Condition 2.

Since only limited clinical data are available regarding Toraymyxin therapy for acute exacerbation of IPF, the efficacy and safety of Toraymyxin, its clinical use, etc. should be carefully assessed through a use-results survey. Data from the survey should be periodically shared with physicians and medical institutions that use Toraymyxin, the related academic society, and PMDA. Through these activities, the applicant should promote further risk mitigation and proper use of Toraymyxin. This should be imposed as Approval Condition 3.

The proposed medical device risk management plan of Toraymyxin is appropriate under the conditional approval system because it plans to ensure the efficacy and safety of Toraymyxin in cooperation with the Japanese Respiratory Society by conducting a use-results survey.

Based on the above results, PMDA has concluded that Toraymyxin may be approved for the intended use as described below. The intended use proposed in the present partial change application is underlined.

Intended Use

Toraymyxin <u>is intended to improve the pathological condition of the following patients:</u>

(1) Patients with a severe pathological condition associated with endotoxemia or suspected gram-negative infection

A severe pathological condition should typically meet at least 2 of the following criteria:

- Body temperature of >38˚C or <36˚C
- Heart rate of >90 beats/min
- Respiratory rate of >20 breaths/min or $PaCO_2$ of <4.3 kPa (32 torr)
- White blood cell count of >12000 cells/mm^3 or <4000 cells/mm^3, or ≥10% stab neutrophils

(2) Patients with acute exacerbation of idiopathic pulmonary fibrosis who have not responded to conventional therapy

Approval Conditions

Acute exacerbation of idiopathic pulmonary fibrosis

1. The applicant is required to develop and appropriately implement a medical device risk management plan.
2. The applicant is required to take necessary actions such as dissemination of information, including the proper use standards prepared in cooperation with the related academic society and other relevant information, to ensure that the product is used, in compliance with the indication, by physicians with adequate knowledge and experience in the treatment of acute exacerbation of idiopathic pulmonary fibrosis after acquiring sufficient skills for using the product and adequate knowledge of possible complications associated with the procedure at medical institutions that have a well-established system for responding to possible complications associated with treatment with the product.
3. The applicant is required to conduct a use-results survey involving all patients treated with the product, periodically report survey results to the Pharmaceuticals and Medical Devices Agency, and promptly take appropriate measures as necessary in cooperation with the related academic society until data from a certain number of patients have been accrued.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 6 years.

PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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