August 22, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Program 2, Software for treatment of disease
Term Name	Software for automated drug delivery for general anesthesia (newly created)
Brand Name	Syringe Pump Control Software for Robotic Anesthesia
Applicant	Nihon Kohden Corporation
Date of Application	September 30, 2021 (Application for marketing approval)

Results of Deliberation

In its meeting held on August 22, 2022, the Subcommittee on Software as a Medical Device of 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 a designation as a medical device that is subjected to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 4 years and 8 months. The product should be approved with the following condition.

Approval Condition

The applicant is required to take measures to ensure that anesthesiologists with sufficient knowledge and experience related to the indication of the product use the product appropriately in accordance with the proper-use guidelines prepared by related academic societies, after obtaining a full understanding of the principle of the product, anesthesia management using the product, emergency response, etc. by attending relevant seminars or through other means.

The brand name of the product should be "Syringe Pump Control Software for Assisting Total Intravenous Anesthesia."

Review Report

August 1, 2022
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	Program 2, Software for treatment of disease
Term Name	Software for automated drug delivery for general anesthesia (to be newly created)
Brand Name	Syringe Pump Control Software for Robotic Anesthesia
Applicant	Nihon Kohden Corporation
Date of Application	September 30, 2021
Reviewing Office	Office of Software as a Medical Device

Review Results

August 1, 2022

Classification	Program 2, Software for treatment of disease
Term Name	Software for automated drug delivery for general anesthesia (to be newly created)
Brand Name	Syringe Pump Control Software for Robotic Anesthesia
Applicant	Nihon Kohden Corporation
Date of Application	September 30, 2021

Results of Review

"Syringe Pump Control Software for Robotic Anesthesia" (hereinafter referred to as Robotic Anesthesia System) is a software program installed in a general-purpose computer and used to control the doses of a sedative (non-proprietary name, propofol), an analgesic (non-proprietary name, remifentanil hydrochloride), and a muscle relaxant (non-proprietary name, rocuronium bromide) by controlling the connected syringe pumps during surgery in general anesthesia with intravenous anesthetics under the supervision of an anesthesiologist. Robotic Anesthesia System provides the automated control of anesthesia by a closed-loop system, which allows the feedback of the patient's Bispectral Index (BIS, which is calculated from electroencephalogram)[i] and the Train-of-four stimulation count (TOF Count)[ii] measured by biological information monitors for an anesthesiologist to check the levels of sedation and muscle relaxation, respectively, as well as the doses of the drugs administered to the patient, thereby determining the rate of administration of propofol, remifentanil hydrochloride, and rocuronium bromide and then controlling the doses administered via the syringe pumps so that both values of the BIS and TOF Count are constant.

The non-clinical data submitted for Robotic Anesthesia System include data on performance and data outlining the implementation status of software development life-cycle process and usability engineering. The data were shown to have no particular problem.

The applicant submitted clinical data form a multicenter, randomized, single-blind, parallel-group, non-inferiority study of Robotic Anesthesia System. The study enrolling patients aged ≥20 years who were to undergo general anesthesia with propofol, remifentanil hydrochloride, and rocuronium bromide was conducted at 5 study sites in Japan.

For the primary endpoint, the percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the time from skin incision to suture completion ("operation time") in a group in which anesthesia management using Robotic Anesthesia System was

[i] The fully awake state is 100 and flat electroencephalogram is 0.
[ii] The minimum level of muscle relaxation is 4 and the maximum one is 0.

performed by an anesthesiologist who can appropriately manage total intravenous anesthesia ("Robotic Anesthesia System group") was compared with that in a group in which anesthesia was managed in a conventional manner ("control group"). The results were 87.21% ± 12.79% for the Robotic Anesthesia System group and 65.19% ± 20.16% for the control group, demonstrating the non-inferiority of Robotic Anesthesia System to the control ($P < 0.001$). The secondary endpoints evaluated included the percentage of time in which sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time, and the results showed the non-inferiority of Robotic Anesthesia System to the control ($P < 0.001$). In addition, the evaluation of the time from the start of anesthesia to skin incision and the time from the end of anesthesia to eye-opening in response to verbal stimuli showed no marked difference between the Robotic Anesthesia System group and the control group. These results led to a conclusion that Robotic Anesthesia System is effective.

Safety data were analyzed. No serious adverse events for which a causal relationship to Robotic Anesthesia System could not be ruled out or malfunctions of Robotic Anesthesia System were reported. However, clinical safety information has been insufficiently collected in the Japanese clinical study, given that the types of surgical procedures using Robotic Anesthesia System in the Japanese clinical study was limited in light of surgical procedures used in clinical settings, that most of the surgeries required a relatively short operation time, and that only 2 subjects with American Society of Anesthesiologists physical status (ASA-PS) 3 were included in the Robotic Anesthesia System group. Therefore, post-marketing information on the incidence of adverse events and malfunctions should be collected continuously through the use-results survey to take risk mitigation measures. In addition, it is important to ensure that the anesthesiologist can manually override the operation of syringe pumps immediately in the event of any problems such as difficulty in anesthesia management using Robotic Anesthesia System. That is, the anesthesiologist must be able to recognize that the condition is unmanageable with Robotic Anesthesia System in an automatic mode, understand information such as the dose controlled by Robotic Anesthesia System, and switch to a manual mode appropriately. To this end, anesthesiologists should become familiar with the operating principle, method of use, trouble shooting, and other aspects of Robotic Anesthesia System, and the development of proper-use guidelines including user training is essential. PMDA concluded that there is no particular safety problem in the automated control of anesthesia by Robotic Anesthesia System if these measures are taken. Given that compliance with the proper-use guidelines prepared by related academic societies is necessary for the safe use of Robotic Anesthesia System, these requirements should be included in the approval condition.

As a result of its review, PMDA has concluded that Robotic Anesthesia System may be approved for the intended use shown below, with the following approval conditions, and that the application should be deliberated at the Subcommittee on Software as a Medical Device.

Intended Use

This software is intended to assist in the administration of total intravenous anesthesia by automatically calculating the doses of propofol, remifentanil hydrochloride, and rocuronium bromide to be delivered to adult patients (excluding patients with ASA-PS ≥4, patients undergoing therapeutic hypothermia during surgery, patients undergoing cardiovascular surgery, and pregnant patients) under total intravenous anesthesia, and by controlling the connected syringe pumps.

Approval Condition

The applicant is required to take measures to ensure that anesthesiologists with sufficient knowledge and experience related to the indication of the product use the product appropriately in accordance with the proper-use guidelines prepared by related academic societies, after obtaining a full understanding of the principle of the product, anesthesia management using the product, emergency response, etc. by attending relevant seminars or through other means.

Review Report

August 1, 2022

Product for Review

Classification	Program 2, Software for treatment of disease
Term Name	Software for automated drug delivery for general anesthesia (to be newly created)
Brand Name	Robotic Anesthesia Software
Applicant	Nihon Kohden Corporation
Date of Application	September 30, 2021
Proposed Intended Use	This software is intended to assist in the administration of total intravenous anesthesia by automatically calculating the doses of anesthetics to be delivered to adult patients under total intravenous anesthesia and by controlling the connected syringe pumps.

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List of Abbreviations

ASA/ASA-PS	ASA physical status
BIS index	Bispectral index
FAS	Full analysis set
SQI	Signal quality indicator
TOF	Train-of-four stimulation
TOF Count	Train-of-four stimulation Count

I. Product Overview

Syringe Pump Control Software for Robotic Anesthesia (hereinafter referred to as Robotic Anesthesia System) is a software program installed in a general-purpose computer and used to control the doses of a sedative (propofol), an analgesic (remifentanil hydrochloride [“remifentanil”]), and a muscle relaxant (rocuronium bromide [“rocuronium”]) by controlling the connected syringe pumps during surgery in general anesthesia with intravenous anesthetics under the supervision of an anesthesiologist (Figures 1 and 2). Robotic Anesthesia System provides the automated control of anesthesia by a closed-loop system, which uses the patient’s Bispectral index (BIS, which is calculated from electroencephalogram) and Train-of-four stimulation count (TOF Count) measured by biological information monitors for an anesthesiologist to check the levels of sedation and muscle relaxation, respectively, to determine the rate of administration of propofol, remifentanil, and rocuronium and then control the doses to be delivered through the syringe pumps so that both values of the BIS and TOF Count are constant (Table 2). This control method simulates part of the anesthesia management conventionally performed by anesthesiologists, and it is not based on a new principle.

Communication via a wired LAN is available between the biological information monitors and Robotic Anesthesia System and between Robotic Anesthesia System and the syringe pumps. Any communication failure is notified by an alarm. The connected biological information monitors and syringe pumps are certified or approved medical devices (Tables 1 and 2). The drugs to be used with Robotic Anesthesia System are propofol (“1% Diprivan Injection-Kit” [Approval number: 21300AMY00077000]), remifentanil (“Ultiva Intravenous 2 mg and Ultiva Intravenous 5 mg” [Approval numbers: 21800AMY10132000 and 21800AMY10133000]), and rocuronium (“Eslax Intravenous 25 mg/2.5 mL and Eslax Intravenous 50 mg/5.0 mL” [Approval numbers: 21900AMX01134000 and 221900AMX01135000]) that have been approved as the brand-name drugs, and the drugs with the same non-proprietary name, dosage form, ingredients and strength (concentration), indications, and dosage and administration as the brand-name drugs. The doses determined by Robotic Anesthesia System are within the range of dosage regimen of propofol, remifentanil, and rocuronium that have been approved as the brand-name drugs (Tables 3, 4, and 5).

In anesthesia management using the automated control of anesthesia by Robotic Anesthesia System, an anesthesiologist must monitor the patient’s condition to ensure that propofol, remifentanil, and rocuronium are being appropriately administered to the patient. Robotic Anesthesia System is equipped with the following features to assist the anesthesiologist in monitoring the patient’s condition: “Automated control system check” function to check communication status at the start of anesthesia to confirm that information necessary for the automated control of anesthesia is available; and the “BIS alarm and TOF Count alarm” function to cause an alarm to go off when the BIS score or TOF Count exceeds the predetermined criterion. If anesthesiologists consider that the condition cannot be managed by Robotic Anesthesia System in an automatic mode, they should stop Robotic Anesthesia System immediately and start the conventional manual operation of the syringe pumps.

In addition to the automated control of anesthesia described above, Robotic Anesthesia System has a manual operation function to enable continuous administration and bolus administration through the syringe pumps controlled by the system software.

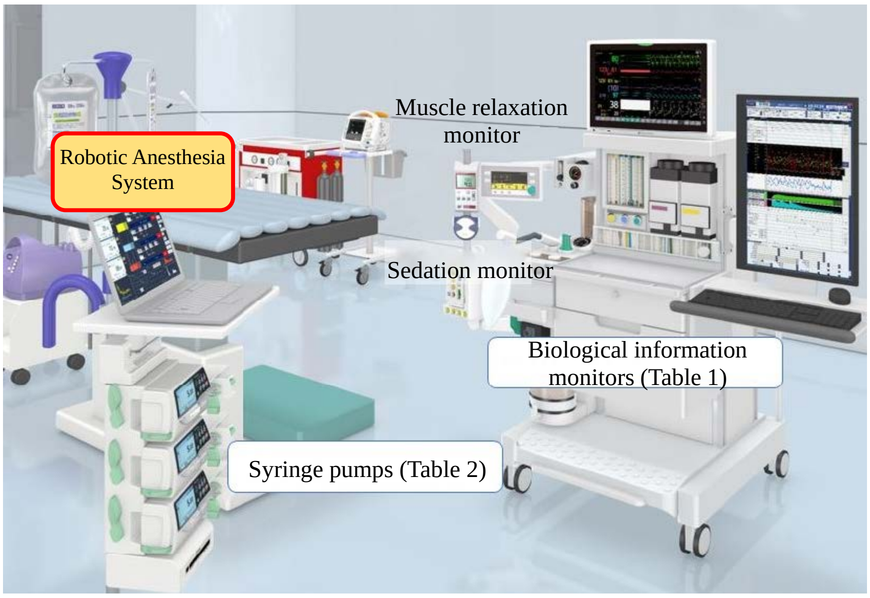


Figure 1. Example of arrangement of syringe pumps and biological information monitors used in combination with Robotic Anesthesia System

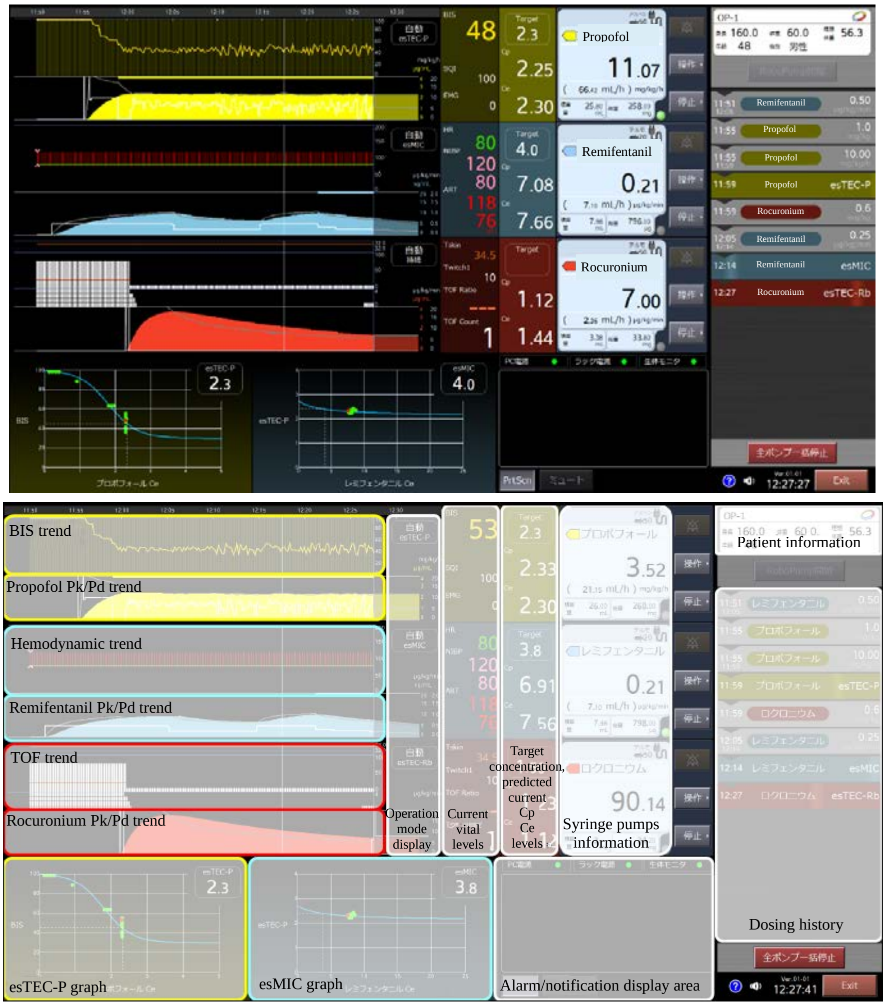


Figure 2. Information that Robotic Anesthesia System displays on general-purpose computer (top) and description of the screen (bottom)

Table 1. Biological information monitors that can be used in combination with Robotic Anesthesia System

Brand name	Approval or Certification number
Bedside Monitor CSM-1000 Series Life Scope G	22500BZX00483000
Bedside Monitor CSM-1000 Series Life Scope G7/5	229ADBZX00128000
Bedside Monitor BSM-6000 Series Life Scope TR	22000BZX01138000

Table 2. Syringe pumps that can be used in combination with Robotic Anesthesia System

Brand name	Approval or Certification number
Terufusion Syringe Pump Type SS 3TCI	23000BZX00021000
Terufusion Syringe Pump Type SS 3	22900BZX00400000
Terufusion Infusion Pump Type LM	22400BZX00229000

Table 3. Automated control of anesthesia by Robotic Anesthesia System for dosage and administration of propofol (brand-name drug)

	Dosage and Administration[iii]	Automated control of anesthesia by Robotic Anesthesia System
Induction	The usual adult dosage is 0.05 mL/kg of Diprivan administered intravenously at the rate of 10 seconds (0.5 mg/kg of propofol every 10 seconds). Diprivan is administered until the patient falls asleep. During the administration, the patient's general condition should be monitored. Diprivan should be administered at a slower rate in patients with ASA[iv] III and IV. Usually, adults fall asleep with 0.20 to 0.25 mL/kg of Diprivan (2.0 to 2.5 mg/kg of propofol). The elderly may fall asleep with a much lower dose. After the patient has fallen asleep, the drug should be additionally administered as needed.	Diprivan (propofol) should be administered at a rate of [redacted] mL/kg every [redacted] seconds for [redacted] seconds. Thereafter, Diprivan should be administered at a rate of [redacted] mg/kg/h until the patient's BIS is ≤[redacted]. Administration at a rate of [redacted] mg/kg/h should be continued for up to [redacted] minutes even if the BIS index does not reach ≤[redacted].
Maintenance	Usually, Diprivan is intravenously administered in combination with oxygen or oxygen/nitrous oxide mixture. The infusion rate should be adjusted according to the patient's general condition so as to achieve an optimal anesthetic depth. In adults, an optimal anesthetic depth can be usually achieved at an infusion rate of 0.4 to 1.0 mL/kg/h of Diprivan (4 to 10 mg/kg/h of propofol). Diprivan should be administered in combination with an analgesic (e.g., narcotic analgesic, local anesthetic). When Diprivan is administered in combination with a local anesthetic, an optimal anesthetic depth can be achieved at a lower dose than usual.	Based on the feedback of the patient's BIS, the target effect-site concentration (described later) should be calculated so that the BIS is [redacted]. Since the difference between the effect-site concentration and blood concentration is small at this stage, the dose should be calculated using the target blood concentration instead of the target effect-site concentration.

[iii] Source: The Dosage and Administration described in the information such as precautions of "1% Diprivan Injection-Kit."

[iv] ASA physical status. A classification according to the American Society of Anesthesiologists, which classifies general condition into 6 classes.

Table 4. Automated control of anesthesia by Robotic Anesthesia System for dosage and administration of remifentanil (brand-name drug)

	Dosage and Administration[v]	Automated control of anesthesia by Robotic Anesthesia System
Induction	The usual dosage is 0.5 µg/kg/min of remifentanil administered as continuous intravenous infusion. The infusion rate should be 1.0 µg/kg/min when strong stimulation is expected during tracheal intubation because of the use of a double lumen tube, difficulty in intubation, and other reasons. Where necessary, a single dose of remifentanil 1.0 µg/kg can be administered intravenously over 30 to 60 seconds before the start of continuous intravenous infusion. However, no single intravenous administration is required if tracheal intubation is performed more than 10 minutes after the start of administration of Ultiva.	Remifentanil should be administered at a rate of [redacted] µg/kg/min.
Maintenance	The usual dosage is 0.25 µg/kg/min of remifentanil administered as continuous intravenous infusion. The infusion rate can be accelerated in the range of 25% to 100% or decelerated in the range of 25% to 50% at intervals of 2 to 5 minutes while monitoring the patient's general condition, but the maximum infusion rate should not exceed 2.0 µg/kg/min. During light anesthesia, a single dose of remifentanil 0.5 to 1.0 µg/kg can be additionally administered intravenously at intervals of 2 to 5 minutes.	Remifentanil should be administered at a rate of [redacted] µg/kg/min after intubation. The rate should be changed to [redacted] µg/kg/min before skin incision and remifentanil should be administered until the predicted effect-site concentration (described later) calculated from the dose of remifentanil is ≥[redacted] ng/mL or [redacted] minutes have passed. Based on the feedback of the patient's BIS, the target effect-site concentration (described later) of remifentanil should be calculated from the balance between the target effect-site concentration of propofol where the BIS is [redacted] and the predicted effect-site concentration of remifentanil. Since the difference between the effect-site concentration and blood concentration is small at this stage, the dose should be calculated using the target blood concentration instead of the target effect-site concentration. The infusion rate may be accelerated in the range of [redacted]% to [redacted]% and decelerated in the range of [redacted]% to [redacted]% at intervals of [redacted] minutes but should be controlled not to exceed the maximum of [redacted] µg/kg/min. During light anesthesia, a single dose of remifentanil [redacted] to [redacted] µg/kg should be additionally administered intravenously at intervals of [redacted] minutes.

[v] Source: The Dosage and Administration described in the information such as precautions of "Ultiva Intravenous 2 mg and Ultiva Intravenous 5 mg."

Table 5. Automated control of anesthesia by Robotic Anesthesia System for dosage and administration of rocuronium (brand-name drug)

Dosage and Administration[vi]	Automated control of anesthesia by Robotic Anesthesia System
The usual adult dosage is 0.6 mg/kg of rocuronium bromide administered intravenously at the time of intubation. An additional dose of 0.1 to 0.2 mg/kg may be administered during surgery, if necessary. Continuous intravenous infusion should be started at the rate of 7 μg/kg/min. The dose may be adjusted according to the patient's age and symptoms, but the maximum intubation dose should be 0.9 mg/kg.	Rocuronium should be administered at [redacted] mg/kg. If the TOF Count does not become [redacted] after [redacted] minutes, an additional dose of [redacted] mg/kg should be administered. If the TOF Count becomes ≥[redacted] after reaching [redacted], rocuronium should be administered at a rate of [redacted] μg/kg/min. After the elapse of [redacted] seconds, the target effect-site concentration (described later) of rocuronium should be determined to calculate the dose so that the TOF Count becomes [redacted].

(1) Principles for calculation of target effect-site concentration of propofol

When the predicted effect-site concentration of propofol from the start to the end of anesthesia is plotted on the x-axis and the BIS on the y-axis, [redacted] (reverse S-shaped) curve is formed. This [redacted] curve plot can be approximated by a logistic regression function. For the [redacted] curve (Figure 3) drawn by this function, the patient's BIS and the predicted target effect-site concentration are fed back every [redacted] seconds to update the [redacted] curve. The target effect-site concentration of propofol is determined so that the BIS on the [redacted] curve is maintained at [redacted].

[redacted]

Figure 3. [redacted] curve showing the effect-site concentration and BIS

(2) Principles for calculation of target effect-site concentration of remifentanil

Propofol and remifentanil are known to have a synergistic effect.[1] The predicted effect-site concentration of remifentanil is plotted on the x-axis and the target effect-site concentration of propofol on the y-axis (Figure 4). As mentioned in (1) above, the target effect-site concentration of propofol is determined so that the BIS is maintained at [redacted]. This curve therefore shows the time when the BIS is 45. For the curve, the predicted effect-site concentration of remifentanil and the target effect-site concentration of propofol are fed back every [redacted] seconds to update the curve. In the automated control of anesthesia by Robotic Anesthesia System, the point at which the deviation from

[vi] Source: The Dosage and Administration described in the information such as precautions of "Eslax Intravenous 25 mg/2.5 mL and Eslax Intravenous 50 mg/5.0 mL."

the neutral point of the curve becomes [redacted] is defined as the target effect-site concentration of remifentanil.

[redacted]

Figure 4. Synergistic effect between propofol and remifentanil

(3) Principles for calculation of target effect-site concentration of rocuronium

After administration of a bolus dose of rocuronium 0.6 mg/kg, the TOF Count, which once disappears, returns to [redacted]. The predicted effect-site concentration of rocuronium at this point is defined as the target effect-site concentration (Figure 5).

[redacted]

Figure 5. Relationship between predicted effect-site concentration of rocuronium and TOF Count

(4) Predicted blood concentrations and predicted effect-site concentrations

The predicted blood concentrations and predicted effect-site concentrations were calculated using a model based on the pharmacokinetics and pharmacodynamics of each drug. [redacted]

[redacted].

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

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

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

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

1.(1) History of development

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

There are approximately 11,700 anesthesiologists in Japan.[7] On the other hand, the annual number of surgeries with general anesthesia in Japan is approximately 2.38 million, showing an increasing trend every year.[8] As it takes a long time for anesthesiologists to be experienced enough to provide high-quality anesthesia care, the lack of anesthesiologists is an ongoing problem.[9] In particular, many anesthesiologists are concentrated in urban hospitals, and hospitals located outside the urban areas continue to have difficulties in securing enough anesthesiologists. As a result, many anesthesiologists are forced to work long hours, and issues related to the working style of anesthesiologists have been pointed out in a survey.[10]

As a step to solve the above issues, Robotic Anesthesia System was developed to automatically calculate the doses of propofol, remifentanil, and rocuronium to be administered to adult patients under total intravenous anesthesia and to control the connected syringe pumps. Robotic Anesthesia System aims to simulate part of the anesthesia management performed conventionally by anesthesiologists and to assist in the administration of total intravenous anesthesia.

1.(2) Use in foreign countries

Robotic Anesthesia System is not approved or licensed in any foreign countries.

2. Specifications

2.(1) Performance and safety specifications

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

The proposed performance specifications for Robotic Anesthesia System include [redacted].
The proposed safety specifications for Robotic Anesthesia System include software life-cycle process and the application of usability engineering to medical device.

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

PMDA reviewed the data stated later in Section "2.(3) Performance" and concluded that there would be no particular problem in the items, test methods, and acceptance criteria of the specifications if [redacted] and [redacted] are included in the performance specifications.

2.(2) Safety specifications

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

The applicant submitted the data indicating a summary of each stage of the life-cycle process required for safety design and maintenance of Robotic Anesthesia System in accordance with IEC 62304:2006/AMD1:2015 "Medical device software - Software life cycle processes" and the data indicating a summary of each stage of the usability engineering in accordance with IEC 62366-1:2015 "Medical devices - Part 1: Application of usability engineering to medical devices."

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

PMDA comprehensively reviewed the submitted data taking into account the discussion presented later in Section "3.B Outline of the review conducted by PMDA" and concluded that there is no particular problem.

2.(3) Performance

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

The applicant submitted the evaluation data relating to the performance of Robotic Anesthesia System indicating that the predicted blood concentrations and predicted effect-site concentrations of propofol, remifentanil, and rocuronium can be calculated and displayed, that the target effect-site concentrations can be calculated, and that the doses of the drugs are calculated and information on the doses is sent to the syringe pumps.

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

PMDA's review of the data on performance is shown below.

1) PMDA requested the applicant to submit the evaluation data relating to [redacted] which can be used when the closed loop system is not used.

2) PMDA requested the applicant to explain the specific features of and evaluation methods for the functions of Robotic Anesthesia System, including the alarm function and the control function to ensure compliance with the dosage regimens of the drugs.

The applicant's response:

1) [redacted], this function will be deleted from this application.

2) Robotic Anesthesia System has safety functions such as [redacted]. These functions will be included in the performance and safety specifications, and the evaluation data on these functions will be submitted.

PMDA's view:

The deletion of [redacted] from this application is reasonable. In addition, the submitted evaluation data including results additionally submitted as the evaluation data for safety functions have demonstrated that the functions of Robotic Anesthesia System, such as the function to control the doses of propofol, remifentanil, and rocuronium, and alarm functions for safety, have been appropriately evaluated. Based on the above, there was no particular problem.

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 Robotic Anesthesia System 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 Ministerial Announcement No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Robotic Anesthesia System to the Essential Principles. Details are shown below.

(1) PMDA's view on the conformity of Robotic Anesthesia System to Article 1, which defines 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 user education and training):

As described later in Section "6.B Outline of the review conducted by PMDA," precautions for the identification of patients eligible for the use of Robotic Anesthesia System and for the automated control of anesthesia by Robotic Anesthesia System are important. Anesthesiologists need to acquire knowledge and skills for these aspects. Thus, an approval condition will be set to take necessary measures such as training for healthcare professionals.

"Robotic Anesthesia Software," the proposed brand name of Robotic Anesthesia System, could imply that a "robot" performs tasks on behalf of humans, which may raise a concern that Robotic Anesthesia System may replace anesthesiologists. In this regard, necessary measures such as providing training for healthcare professionals should be taken before the use of Robotic Anesthesia System. Furthermore, the word "robot" often refers to a system that has sensors, controls, and drives, and therefore it may mislead people into thinking that Robotic Anesthesia System itself has sensors and drives. For this reason, the brand name should be changed to "Syringe Pump Control Software for Robotic Anesthesia."

(2) PMDA's view on the conformity of Robotic Anesthesia System to Article 2, which defines the 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 "7.B Outline of the review conducted by PMDA," data from clinical studies are limited in terms of patients and surgical procedures as compared to surgeries in which general anesthesia is administered with propofol, remifentanil, and rocuronium in clinical practice. Thus, PMDA determined it necessary to continue to collect post-marketing safety information and instructed the applicant to conduct a use-results survey.

(3) PMDA's view on the conformity of Robotic Anesthesia System to Article 3, which defines the performance and function of medical devices, and to Article 6, which defines the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," general anesthesia was administered using Robotic Anesthesia System in the clinical study which confirmed the appropriate effects of sedation, analgesia, and muscle relaxation. There was no problem with the conformity of Robotic Anesthesia System to Articles 3 and 6.

(4) PMDA's view on the conformity of Robotic Anesthesia System to Article 12, which defines the requirements for software development life cycle for medical devices:
As described earlier in Section "2.(1).B Outline of the review conducted by PMDA" and Section "2.(2).B Outline of the review conducted by PMDA," Robotic Anesthesia System has been developed appropriately based on the software life-cycle process and has been shown to operate adequately. The software development life cycle has been justified.

(5) PMDA's view on the conformity of Robotic Anesthesia System to Article 17, which defines the requirements for information provision to users by publishing or providing information on precautions, etc. in the instructions for use and other documents ("Information on Precautions, etc."):
As described later in Section "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," users must understand the principle of Robotic Anesthesia System, identify the eligible patients, and use the device properly in order to maintain the

risk-benefit balance of Robotic Anesthesia System. The applicant, therefore, should provide information to users through the Information on Precautions, etc., proper-use guidelines, and training, or by other means

PMDA comprehensively reviewed the conformity of Robotic Anesthesia System 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 data summarizing the risk management system and risk management activities implemented for Robotic Anesthesia System in accordance with JIS T 14971: 2012 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA's review of the document on risk management is shown below.

Robotic Anesthesia System operates while communicating data between Robotic Anesthesia System and the biological information monitors and between Robotic Anesthesia System and the syringe pumps. PMDA asked the applicant to explain ensuring cybersecurity.

The applicant's response:
Ensuring cybersecurity was evaluated in accordance with "Guidance on Ensuring Cyber Security of Medical Devices" (PSEHB/MDED Notification No. 0724-1 and PSEHB/PSD Notification No. 0724-1, dated July 24, 2018). The use of Robotic Anesthesia System in external connection settings was analyzed, and cybersecurity measures were taken for individual interfaces in which the possibility of cyber risk was detected. As a result of the above measures, the security risks of Robotic Anesthesia System harmful to healthcare professionals, patients, assets, and environment have been reduced to the possible extent. The result is acceptable.

PMDA comprehensively reviewed the document on risk management taking into account the applicant's explanation about ensuring cybersecurity and 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

The applicant did not submit data on the manufacturing process of Robotic Anesthesia System, in accordance with the Notification "Handling of Medical Device Software" (PFSB/MDRMPE Notification No. 1121-33, PFSB/SD Notification No. 1121-1, and PFSB/CND Notification No. 1121-29, dated November 21, 2014).

5.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of data on the manufacturing process of Robotic Anesthesia System, in accordance with the above notification.

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

6.A Summary of the data submitted

6.A.(1) Study design

A multicenter, randomized, single-blind, parallel-group, non-inferiority study was conducted to evaluate the efficacy and safety of Robotic Anesthesia System (hereinafter referred to as “Japanese clinical study,” Table 6). The Japanese clinical study enrolled patients aged ≥20 years who were to undergo general anesthesia with propofol, remifentanil, and rocuronium. The percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the time from skin incision to suture completion (“operation time”) in a group in which anesthesia is managed with Robotic Anesthesia System (“Robotic Anesthesia System group”) was compared with that in a group in which anesthesia is managed in a conventional manner by an anesthesiologist who can appropriately administer total intravenous anesthesia (“control group”)). Table 7 shows the definition of “time in which sedation, analgesia, and muscle relaxation were appropriately maintained.” Anesthesia was managed by anesthesiologists who were educated and trained on the devices to be used and who were able to administer total intravenous anesthesia independently and appropriately.

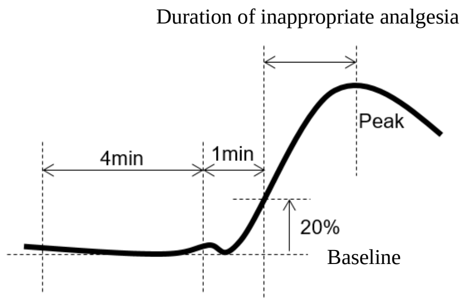
Subjects were randomly assigned at a 1:1 ratio to the Robotic Anesthesia System group or the control group, and a total of 123 subjects (63 in the Robotic Anesthesia System group and 60 in the control group) were enrolled (Figure 6). Three subjects were excluded from the safety analysis set for the following reasons: The subject met the exclusion criterion 3 shown in Table 6 (1 subject); and the subject requested discontinuation (2 subjects). One subject was excluded from the full analysis set (FAS). The reason for exclusion was that the syringe pumps for remifentanil and rocuronium were found to have been set in reverse order before intubation.

Table 6. Summary of the Japanese clinical study

Item	Outline
Objective	To demonstrate the efficacy and safety of Robotic Anesthesia System in patients who were to receive general anesthesia with propofol, remifentanil, and rocuronium versus a control group in which anesthesia is managed in a conventional manner by anesthesiologists who administer total intravenous anesthesia routinely in clinical practice and are able to manage total intravenous anesthesia independently and appropriately in a randomized, comparative, non-inferiority study.
Type of the study	Multicenter, randomized, single-blind, parallel-group, non-inferiority study
Study population	Patients who were to undergo general anesthesia with propofol, remifentanil, and rocuronium
Sample size	123 (63 in the Robotic Anesthesia System group and 60 in the control group)
Major inclusion criteria	1. Men and women aged ≥20 years at the time of informed consent 2. Patients with ASA physical status (ASA-PS) 1 to 3 and receiving planned general anesthesia with propofol, remifentanil, and rocuronium 3. Patients giving written consent based on their own free will after being fully informed of participation in the Japanese clinical study and fully understanding it
Major exclusion criteria	1. Patients with a history of hypersensitivity to propofol, remifentanil, rocuronium, or sugammadex sodium (rocuronium antagonist) 2. Patients to whom the BIS sensor cannot be attached during surgery 3. Patients who cannot receive additional doses of rocuronium after the initial single dose 4. Patients in whom non-invasive blood pressure cannot be measured during surgery 5. Patients who undergo therapeutic hypothermia during surgery 6. Patients who undergo cardiovascular surgery 7. Patients who undergo nerve block during surgery 8. Pregnant or nursing women 9. Patients who have participated in any other clinical study within 12 weeks before informed consent or patients who intend to participate in any other clinical study during the period of participation in the Japanese clinical study 10. Patients who are considered by the investigator or sub-investigator of the Japanese clinical study to be ineligible for enrollment in the Japanese clinical study
Primary endpoint	Percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time
Secondary endpoints	1. Percentage of the time in which sedation was appropriately maintained during the operation time 2. Percentage of the time in which analgesia was appropriately maintained during the operation time 3. Percentage of the time in which muscle relaxation was appropriately maintained during the operation time 4. Percentage of the time in which both sedation and analgesia were appropriately maintained during the operation time 5. Percentage of the time in which both sedation and muscle relaxation were appropriately maintained during the operation time 6. Percentage of the time in which the BIS score was maintained in the target range (The BIS ≥35 and ≤55. Not applied if the SQI is <80 where the BIS score is less reliable due to noise from electrocautery, etc.) 7. Time from administration of an antagonist of muscle relaxants (sugammadex) to return to a TOF ratio[vii] ≥0.9 8. Time from the end of propofol administration to awakening from anesthesia (No significance level is established for Nos. 7 and 8.)
Safety endpoints	Adverse events, malfunctions of the device used in the Japanese clinical study
Number of study sites	5 study sites

[vii] The ratio between the response to the first (T1) and fourth (T4) train-of-four stimulation.

Table 7. Definition of time in which sedation, analgesia, and muscle relaxation were appropriately maintained

Appropriate level of sedation	The BIS ≥35 and ≤55. However, if the SQI is <80 where the BIS score is less reliable due to noise from electrocautery, etc., the anesthesiologist will determine the level of sedation. (Rationale) A BIS score of ≥35 and ≤55, which is the maintenance target during surgery with total intravenous anesthesia, was selected to as an appropriate level of sedation.
Appropriate level of analgesia	The absence of sudden changes in circulation (increases in systolic blood pressure and heart rate). However, such changes will not be evaluated for 5 minutes after administration and dose modification of circulatory agonists, which directly affect blood pressure and heart rate. A sudden change in circulation refers to increases in systolic blood pressure and heart rate by 20% from the 4-minute mean.  Sudden change in circulation (Rationale) The absence of sudden changes in circulation (increases in systolic blood pressure and heart rate) was selected, because this parameter is used as a means by anesthesiologists to check the status of analgesia in clinical settings.
Appropriate level of muscle relaxation	Moderate muscle relaxation (TOF Count = 1). (Rationale) TOF Count, which is measured by the muscle relaxation monitor, is a parameter that anesthesiologists generally use as an indicator of the state of muscle relaxation during surgery. Moderate muscle relaxation (TOF Count = 1), which corresponds to surgical muscle relaxation, was selected as an appropriate status of muscle relaxation.

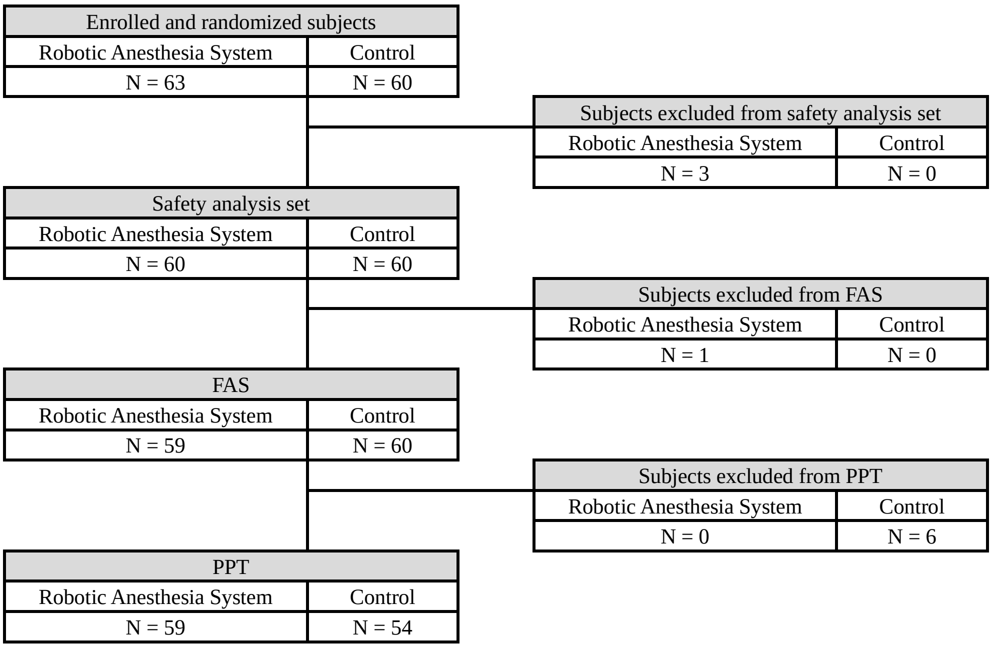


Figure 6. Disposition of analysis population

6.A.(2) Patient characteristics

Table 8 shows a summary of the baseline characteristics and demographics of patients included in the Japanese clinical study, Table 9 shows surgeries performed, and Table 10 shows major surgical procedures.

Table 8. Baseline characteristics and demographics of subjects

		Robotic Anesthesia System (N = 60)	Control (N = 60)	*P* value
Sex	[redacted]			1.000
	Male	18 (30.0%)	17 (28.3%)	
	Female	42 (70.0%)	43 (71.7%)	
Age at informed consent (years)	[redacted]			0.638
	Mean	54.5	55.7	
	Standard deviation	14.9	14.9	
	Minimum	21	20	
	Median	53.0	54.0	
	Maximum	81	83	
Height (cm)	[redacted]			0.548
	Mean	160.52	159.56	
	Standard deviation	8.28	9.13	
	Minimum	144.0	140.0	
	Median	160.35	158.00	
	Maximum	180.0	179.4	
Weight (kg)	[redacted]			0.860
	Mean	60.37	59.97	
	Standard deviation	12.79	11.92	
	Minimum	39.3	36.9	
	Median	56.95	59.05	
	Maximum	93.5	85.5	
BMI	[redacted]			0.843
	Mean	23.29	23.42	
	Standard deviation	3.82	3.58	
	Minimum	16.3	17.4	
	Median	22.26	22.86	
	Maximum	34.5	34.7	
ASA-PS	[redacted]			0.886
	1	23 (38.3%)	20 (33.3%)	
	2	35 (58.3%)	38 (63.3%)	
	3	2 (3.3%)	2 (3.3%)	

Table 9. Operation time for FAS (min)

	Robotic Anesthesia System (N = 59)	Control (N = 60)
Mean	151.1	173.7
Standard deviation	69.7	78.1
Minimum	51	68
Median	135.0	161.0
Maximum	399	399

Table 10. Major surgical procedures

Robotic Anesthesia System	Control
Arthroscopic rotator cuff repair Hip replacement Open surgery for fracture (radius) Removal of foreign body in bone	Arthroscopic rotator cuff repair Total knee replacement Open surgery for fracture (scapula/radius) Ligament reconstruction Removal of foreign body in bone
Stent graft placement (abdominal aorta) Stent graft placement (iliac artery) Iliac artery embolization Femoral endarterectomy	Stent graft placement (abdominal aorta)
Robotic-assisted partial nephrectomy Robotic-assisted radical prostatectomy Laparoscopic radical prostatectomy Laser transurethral resection of the prostate Transurethral resection of bladder tumor Laparoscopic adrenalectomy	Laparoscopic surgery for malignancy in the kidney (ureter) Robotic-assisted radical prostatectomy Laparoscopic radical prostatectomy Laser transurethral resection of the prostate
Radical hysterectomy Open total hysterectomy Total vaginal hysterectomy Robotic total hysterectomy Laparoscopic simple total hysterectomy Laparoscopic uterine myomectomy (enucleation) and laparoscopic debulking surgery for uterine adenomyosis Laparoscopic sacrocolpopexy Laparoscopic adnexectomy or salpingectomy Laparoscopic ovarian cystectomy	Total vaginal hysterectomy and colpocleisis Robotic total hysterectomy Robotic modified radical hysterectomy Laparoscopic simple total hysterectomy Laparoscopic total vaginal hysterectomy Laparoscopic uterine myomectomy and removal of fallopian tube tumor Laparoscopic adnexectomy Laparoscopic surgery for removal of adnexal tumor Laparoscopic sacrocolpopexy Laparoscopic sacrocolpopexy and total vaginal hysterectomy Laparoscopic ovarian cystectomy Le Fort colpocleisis
Mastectomy Partial mastectomy Pectoral muscle-conserving mastectomy	Partial mastectomy Pectoral muscle-conserving mastectomy
Laparoscopic inguinal hernia repair Laparoscopic right hemicolectomy	Laparoscopic resection of colon cancer Laparoscopic cholecystectomy Laparoscopic low anterior resection and stoma formation Laparoscopic right hemicolectomy Thoracoscopic partial lung resection
Parathyroid adenomectomy Total thyroidectomy Lymphatic anastomosis and liposuction Neck dissection	Left thyroid lobectomy and subclavian lymphadenectomy Skin tumor resection

6.A.(3) Study results

6.A.(3).1) Efficacy endpoints

Table 11 shows the results of the primary and secondary endpoints.

The “percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time,” the primary endpoint, in the FAS analysis, was 87.21% ± 12.79% in the Robotic Anesthesia System group and 65.19% ± 20.16% in the control group, demonstrating the non-inferiority of Robotic Anesthesia System to the control ($P < 0.001$).

Table 11. Results of efficacy endpoints (mean ± standard deviation)

	Robotic Anesthesia System	Control	*P* value
Primary endpoint			
Percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time	87.21 ± 12.79%	65.19 ± 20.16%	<0.001
Secondary endpoints			
1. Percentage of time in which sedation was appropriately maintained during the operation time	96.39 ± 4.49%	89.94 ± 13.98%	<0.001
2. Percentage of time in which analgesia was appropriately maintained during the operation time	99.56 ± 1.86%	99.93 ± 0.41%	<0.001
3. Percentage of time in which muscle relaxation was appropriately maintained during the operation time	90.84 ± 12.60%	72.34 ± 20.03%	<0.001
4. Percentage of time in which both sedation and analgesia were appropriately maintained during the operation time	96.05 ± 4.73%	89.87 ± 13.95%	<0.001
5. Percentage of time in which both sedation and muscle relaxation were appropriately maintained during the operation time	87.53 ± 12.81%	65.26 ± 20.19%	<0.001
6. Percentage of time in which the BIS score was maintained in the target range during the operation time	96.23 ± 4.93%	88.08 ± 17.47%	<0.001
7. Time from administration of an antagonist of muscle relaxants (sugammadex) to return to a TOF ratio ≥0.9	2.514 ± 1.171 min	2.490 ± 1.163 min	-
8. Time from the end of propofol administration to awakening from anesthesia (first eye-opening in response to verbal stimuli)	9.418 ± 3.637 min	8.404 ± 4.353 min	-

6.A.(3).2) Safety endpoints

The overall incidence of adverse events during the intraoperative observation and postoperative observation periods was 90.0% (54 subjects) in the Robotic Anesthesia System group and 100% (60 subjects) in the control group (Table 12). Adverse events for which a causal relationship to the device used in the Japanese clinical study could not be ruled out occurred in 3 subjects (5.0%) in the Robotic Anesthesia System group and in 2 subjects (3.3%) in the control group (Table 13). Common adverse events were procedural pain in 48 subjects (80.0%) in the Robotic Anesthesia System group and 55 subjects (91.7%) in the control group, and nausea in 14 subjects (23.3%) in the Robotic Anesthesia System group and 15 subjects (25.0%) in the control group. When more than one adverse event occurred in one subject or the same adverse event occurred more than once in one subject, the number of subjects was counted as one.

No malfunctions of Robotic Anesthesia System were reported during the Japanese clinical study.

Table 12. Tabulation of all adverse events during the intraoperative observation and postoperative observation periods (safety analysis)

System Organ Class - Preferred Term	Robotic Anesthesia System (N = 60)			Control (N = 60)		
	No. of events	n	Incidence (%)	No. of events	n	Incidence (%)
Overall	125	54	90.0	139	60	100.0
Cardiac disorders	0	0	0.0	1	1	1.7
- Bradycardia	0	0	0.0	1	1	1.7
Gastrointestinal disorders	24	21	35.0	25	23	38.3
- Abdominal pain	0	0	0.0	2	2	3.3
- Abdominal pain upper	1	1	1.7	0	0	0.0
- Constipation	1	1	1.7	1	1	1.7
- Gastritis	0	0	0.0	1	1	1.7
- Nausea	14	14	23.3	15	15	25.0
- Vomiting	8	8	13.3	6	6	10.0
General disorders and administration site conditions	18	12	20.0	19	14	23.3
- Chills	14	9	15.0	11	7	11.7
- Pain	0	0	0.0	1	1	1.7
- Pyrexia	4	4	6.7	4	4	6.7
- Catheter site pain	0	0	0.0	1	1	1.7
- Inflammation	0	0	0.0	2	2	3.3
Injury, poisoning and procedural complications	51	48	80.0	62	56	93.3
- Post procedural haemorrhage	0	0	0.0	3	3	5.0
- Inflammation of wound	1	1	1.7	0	0	0.0
- Bladder injury	1	1	1.7	2	2	3.3
- Procedural pain	48	48	80.0	55	55	91.7
- Procedural dizziness	1	1	1.7	1	1	1.7
- Vulvovaginal injury	0	0	0.0	1	1	1.7
Investigations	4	4	6.7	8	8	13.3
- Blood pressure increased	0	0	0.0	1	1	1.7
- C-reactive protein increased	0	0	0.0	1	1	1.7
- Blood urine present	0	0	0.0	1	1	1.7
- Oxygen saturation decreased	0	0	0.0	2	2	3.3
- Urine output decreased	4	4	6.7	3	3	5.0
Metabolism and nutrition disorders	0	0	0.0	1	1	1.7
- Hypoglycaemia	0	0	0.0	1	1	1.7
Musculoskeletal and connective tissue disorders	3	3	5.0	2	2	3.3
- Back pain	1	1	1.7	1	1	1.7
- Musculoskeletal pain	2	2	3.3	1	1	1.7
Nervous system disorders	4	4	6.7	2	2	3.3
- Headache	3	3	5.0	1	1	1.7
- Hypoaesthesia	1	1	1.7	1	1	1.7
Psychiatric disorders	8	8	13.3	2	2	3.3
- Delirium	2	2	3.3	0	0	0.0
- Insomnia	6	6	10.0	2	2	3.3
Renal and urinary disorders	1	1	1.7	2	2	3.3
- Ketonuria	0	0	0.0	1	1	1.7
- Urinary retention	0	0	0.0	1	1	1.7
- Bladder spasm	1	1	1.7	0	0	0.0
Reproductive system and breast disorders	8	8	13.3	11	11	18.3
- Genital haemorrhage	8	8	13.3	11	11	18.3
Respiratory, thoracic and mediastinal disorders	2	2	3.3	0	0	0.0
- Sputum increased	1	1	1.7	0	0	0.0
- Oropharyngeal pain	1	1	1.7	0	0	0.0
Skin and subcutaneous tissue disorders	1	1	1.7	3	3	5.0
- Erythema	1	1	1.7	1	1	1.7
- Pruritus	0	0	0.0	1	1	1.7
- Skin exfoliation	0	0	0.0	1	1	1.7
Vascular disorders	1	1	1.7	1	1	1.7
- Hypertension	1	1	1.7	1	1	1.7

Table 13. Breakdown of adverse events for which a causal relationship to the investigational device could not be ruled out and causes of events

Group	Event	Severity	Serious or non-serious	Medical treatment	Causality
Control	Abdominal pain	Moderate	Non-serious	Famotidine D Tablets	Unknown
Control	Pyrexia	Moderate	Non-serious	Loxoprofen Tablets	Unknown
	Hypertension	Moderate	Non-serious	Nifedipine CR Tablets Frandol Tape	Unknown
	Headache	Moderate	Non-serious	Loxoprofen Tablets	Unknown
Robotic Anesthesia System	Headache	Moderate	Non-serious	Calonal Tablets	Unknown
	Pyrexia	Mild	Non-serious	None	Unknown
Robotic Anesthesia System	Insomnia	Moderate	Non-serious	Atarax-P Parenteral Solution	Unknown
Robotic Anesthesia System	Pyrexia	Mild	Non-serious	None	Unknown

6.B Outline of the review conducted by PMDA

Taking account of the comments from the Expert Discussion, PMDA focused on the following points during the review.

6.B.(1) Clinical significance of Robotic Anesthesia System

The applicant's explanation about the clinical significance of Robotic Anesthesia System:
The lack of anesthesiologists in Japan has been described earlier in Section "1.(1) History of development."

Robotic Anesthesia System calculates the necessary amounts of a sedative, an analgesic, and a muscle relaxant for patients by calculating the target blood concentration and target effect-site concentration of the intravenous anesthetics based on the feedback of the BIS score and TOF Count from the biological information monitors and information on the dose delivered by the connected syringe pumps under the supervision of anesthesiologists. In accordance with these calculation results, the setting of the syringe pumps is controlled to maintain total intravenous anesthesia. The use of Robotic Anesthesia System allows anesthesiologists to focus on better patient management as the operations conventionally performed by anesthesiologists, such as flow rate setting for syringe pumps, can be carried out by Robotic Anesthesia System. The use of Robotic Anesthesia System could result in a reduction in the risks of human errors associated with anesthesiologists' fatigue during prolonged surgery.

PMDA's view:
The applicant explained that Robotic Anesthesia System would reduce the burden on anesthesiologists. However, Robotic Anesthesia System is unlikely to shorten the working hours of anesthesiologists because it is used under the supervision of anesthesiologists. On the other hand, Robotic Anesthesia System may possibly assist anesthesiologists in their tasks by performing some of various tasks for which anesthesiologists are responsible during surgery under intravenous anesthesia, such as monitoring of the BIS score and TOF Count and operation of syringe pumps. Although the Japanese clinical study was not conducted under a protocol that aimed to verify the usefulness of the anesthesia management using Robotic Anesthesia System versus conventional anesthesia management alone, the study demonstrated that anesthesia was managed at a level similar to the conventional anesthesia management as described later in Section "6.B.(2) Efficacy of Robotic Anesthesia System."

The occurrence of human errors is unavoidable in operations involving humans. The use of Robotic Anesthesia System was not shown to reduce human errors in the Japanese clinical study, but PMDA understands the applicant's view that the assistance of Robotic Anesthesia System in anesthesiologists' tasks will lead to a reduction in operations involving human intervention, which may consequently reduce the risks of human errors.

Based on the above, PMDA has concluded that Robotic Anesthesia System has clinical significance in assisting anesthesiologists in their tasks.

6.B.(2) Efficacy of Robotic Anesthesia System

PMDA's view:

Anesthesia management during surgery can be divided into the following 3 phases: The phase up to the patient's loss of consciousness ("induction phase"), the phase of maintaining the patient's anesthetic state ("maintenance phase"), and the phase at which the patient awakes after surgery ("awakening phase"). Given that Robotic Anesthesia System is a product used for administration of a series of anesthetics from the start to the end of anesthesia (Table 3 to Table 5), the efficacy of Robotic Anesthesia System should be evaluated in the induction phase, the maintenance phase, and the awakening phase. In the Japanese clinical study, however, the target time for efficacy evaluation was defined as the time from skin incision to suturing (operation time). PMDA asked the applicant to explain the efficacy evaluation for the induction phase that was not included in the primary or secondary endpoints of the Japanese clinical study.

The applicant's response:

No efficacy endpoints in the induction phase were specified in the Japanese clinical study. Therefore, the induction phase was defined as the time from the start of anesthesia to the start of skin incision to perform additional analyses for the induction time and the percentage of time in which sedation, analgesia, and muscle relaxation were appropriately maintained from the start of anesthesia to the start of skin incision.

The time from the start of anesthesia to the start of skin incision was 42.70 ± 9.27 minutes in the Robotic Anesthesia System group (N = 59) and 44.04 ± 10.62 minutes in the control group (N = 59; 1 of 60 subjects in the FAS had missing data for the induction phase); the percentage of time in which sedation was appropriately maintained was 85.17% ± 10.58% in the Robotic Anesthesia System group (N = 59) and 68.13% ± 18.60% in the control group (N = 59); the percentage of time in which analgesia was appropriately maintained was 97.83% ± 6.50% in the Robotic Anesthesia System group (N = 59) and 98.30% ± 4.18% in the control group (N = 59); and the percentage of time in which muscle relaxation was appropriately maintained was 93.81% ± 18.26% in the Robotic Anesthesia System group (N = 59) and 88.69% ± 12.84% in the control group (N = 59). These results suggest that the efficacy of Robotic Anesthesia System in the anesthesia induction phase is comparable to that of the control.

PMDA's view:
As shown in 1) to 5) below, there was no particular problem with the efficacy of the automated control of anesthesia by Robotic Anesthesia System based on the results of the Japanese clinical study and the applicant's response.

1) Definition of appropriate sedation, analgesia, and muscle relaxation

In clinical practice, anesthesia is managed to maintain an appropriate state of sedation where the BIS is ≥35 and ≤55, and an appropriate state of muscle relaxation is defined as moderate muscle relaxation (TOF Count = 1), which corresponds to surgical muscle relaxation. In light of these factors, PMDA considers it reasonable to use the same state of sedation and muscle relaxation to define the appropriate state in the Japanese clinical study. On the other hand, there is no index to evaluate the analgesic state at present, and therefore it is difficult to define the appropriate state of analgesia based on the management method used in clinical practice. However, it is known that inadequate sedation and analgesia results in sympathetic dominance due to pain, leading to increased blood pressure and heart rate. It is therefore reasonable to define appropriate analgesia as the absence of changes in circulation such as rapid increases in systolic blood pressure and heart rate. Based on the above, the definitions of appropriate sedation, analgesia, and muscle relaxation in the Japanese clinical study are reasonable.

2) Efficacy in the induction phase

There was no particular problem with the efficacy of Robotic Anesthesia System in the induction phase, because the applicant's response showed similar results for the time from the start of anesthesia to skin incision and the percentage of time in which sedation, analgesia, and muscle relaxation were appropriately maintained.

3) Efficacy in the maintenance phase

There was no particular problem with the efficacy of Robotic Anesthesia System in the maintenance phase, because the primary endpoint and secondary endpoints 1 to 6 of the Japanese clinical study demonstrated the non-inferiority of Robotic Anesthesia System to the control.

4) Efficacy in the awakening phase

The efficacy of Robotic Anesthesia System in the awakening phase was evaluated based on the time from the end of propofol administration to awakening from anesthesia (first eye-opening in response to verbal stimuli) as the secondary endpoint 8 of the Japanese clinical study. Results showed no marked difference between the Robotic Anesthesia System group and the control group. Because the timing of the start of verbal stimuli was not defined in the Japanese clinical study, the results are unlikely to reflect a stringent comparison between the Robotic Anesthesia System group and the control group. However, given that the patient's condition changes every moment during the awakening phase, evaluation using the time from the end of propofol administration to eye-opening in response to verbal stimuli (the patient's name called at the discretion of the anesthesiologist) is possible. Therefore, there was no particular problem with the efficacy of Robotic Anesthesia System in the awakening phase.

5) Combination of automated control of anesthesia by Robotic Anesthesia System and manual operation of syringe pumps by anesthesiologists

The applicant's explanation about the combination of automated control of anesthesia by Robotic Anesthesia System and manual operation of syringe pumps by anesthesiologists:

The Japanese clinical study evaluated the efficacy and safety of the automated control of the 3 drugs (sedative, analgesic, and muscle relaxant drugs) administered by Robotic Anesthesia System. The combination of the automated control of anesthesia by Robotic Anesthesia System and manual operation by anesthesiologists is also assumed in clinical practice. Examples of the combination are shown in Table 14.

The administration of a muscle relaxant by Robotic Anesthesia System is controlled automatically based on the feedback of the TOF Count and the dose of the muscle relaxant. Muscle relaxant administration is controlled separately from the automated administration of sedative and analgesic drugs. Therefore, switching to manual mode for administration of the muscle relaxant is unlikely to affect the automated administration of sedative and analgesic drugs (Table 14 [a] and [c]). The operating principle of the automated administration of analgesics by Robotic Anesthesia System is based on the fact that there is a synergistic effect between sedative and analgesic drugs. The automated administration of the analgesic requires calculation based on the automated administration of the sedative [see earlier Section "I.(2) Principles for calculation of target effect-site concentration of remifentanil"]. On the other hand, the administration of the sedative is controlled automatically based on the feedback of the BIS score and the dose of the sedative. When the sedative and analgesic drugs are co-administered, it is not possible to administer the analgesic only in an automatic mode (Table 14 [b], [c], and [d]). Manual operation of syringe pumps by anesthesiologists represents anesthesia management that has been conventionally performed by anesthesiologists.

Table 14. Combination of automated control of anesthesia by Robotic Anesthesia System and manual operation of syringe pumps by anesthesiologists

	Sedative	Analgesic	Muscle relaxant	Reason for combination
(a)	Automated	Automated	Manual	No muscle relaxants may be administered during surgery.
(b)	Automated	Manual	Automated	Analgesics other than remifentanil are used.
(c)	Automated	Manual	Manual	No muscle relaxants may be administered during surgery. Analgesics other than remifentanil are used.
(d)	Manual	Manual	Automated	Inhalation anesthesia is administered for sedation. Sedatives other than propofol are used.

PMDA's view:

According to the table above, manual operation by anesthesiologists will be necessary if drugs other than those used in the Japanese clinical study are used in clinical practice. In this case, the BIS score and TOF Count may be affected by differences in the interactions, etc. related to drug disposition between the drugs used in the Japanese clinical study and other drugs. To assess the impact of the affected BIS score and TOF Count on the automated control of anesthesia by Robotic Anesthesia System, PMDA asked the applicant to explain whether the increase of risks such as overdose or underdose is within a clinically acceptable range.

The applicant's response:
Although the impact on the BIS score varies depending on the type of analgesics used concomitantly, the dose of a sedative is controlled by Robotic Anesthesia System based on the target effect-site concentration of the sedative calculated from the value obtained by the feedback of the BIS score after the administration of the sedative and analgesic drugs. For example, if there is a large decrease in the BIS score due to the effect of an analgesic other than remifentanil, Robotic Anesthesia System will provide a value to lower the target effect-site concentration of a sedative (propofol), thereby controlling syringe pumps to decrease the dose of the sedative. Even if the pharmacokinetic models of sedative and analgesic drugs are affected by the synergistic effect between the drugs, the automated administration of the sedative by Robotic Anesthesia System should not result in overdose or underdose as a principle. Therefore, there will be no clinically unacceptable increase in the risks of overdose or underdose. To date, there have been no reports that sedatives or analgesics affect muscle relaxation determined by the TOF Count. There will also be no clinically unacceptable increase in risks for the effect on the automated control of muscle relaxation.

PMDA's view:
Since Robotic Anesthesia System automatically controls the infusion rate by monitoring the BIS score and TOF Count as the indicators of the patient's condition, PMDA understands the applicant's explanation that the immediate risks of overdose or underdose are low even if there is an interaction between a sedative and an analgesic. However, when the use of drugs other than propofol, remifentanil, or rocuronium results in the addition of a factor affecting pharmacokinetics, there is no evidence such as clinical study data supporting the efficacy and safety of the automated control of anesthesia by Robotic Anesthesia System. It is unclear whether the dose can be appropriately maintained in the presence of interactions between drugs.

PMDA instructed the applicant to (a) inform healthcare professionals that there is no evidence indicating that any drug not used in the Japanese clinical study can be used with the automated control of anesthesia by Robotic Anesthesia System and to examine whether such drugs can be used with the automated control of anesthesia by Robotic Anesthesia System by checking the interactions of the drugs based on the Information on Precautions, etc. of the drugs and known literature, etc., and (b) provide precautions through the Information on Precautions, etc. to advise healthcare professionals to ensure that the drugs are used with careful monitoring of the patient's condition when used with the automated control of anesthesia by Robotic Anesthesia System. The applicant responded to these instructions.

6.B.(3) Safety of Robotic Anesthesia System

PMDA's view:
No serious adverse events for which a causal relationship to Robotic Anesthesia System could not be ruled out or malfunctions of Robotic Anesthesia System were reported in the Japanese clinical study. However, clinical safety information has been insufficiently collected in the Japanese clinical study, given that the type of surgical procedures used in the Robotic Anesthesia System group in the clinical study was limited, that most of the surgeries required a relatively short operation time with the mean of 151.1 minutes and the median of 135 minutes, and that only 2 subjects with ASA-PS 3 were

included in the Robotic Anesthesia System group. Therefore, post-marketing information on the incidence of adverse events and malfunctions should be collected continuously through the use-results survey to take risk mitigation measures.

To ensure the safety of Robotic Anesthesia System, anesthesiologists should be able to manually control the state of anesthesia in a conventional manner in the event of any problem such as difficulty in the automated control of anesthesia by Robotic Anesthesia System. For this reason, PMDA asked the applicant to explain the procedure necessary for anesthesiologists to manually control the state of anesthesia in case of emergency.

The applicant's response:
If Robotic Anesthesia System fails to appropriately provide automated anesthesia, anesthesiologists should stop the automated control of anesthesia by Robotic Anesthesia System on their discretion to manually override the operation of syringe pumps. As problems with the automated control of anesthesia by Robotic Anesthesia System, the following cases are assumed:

(a) biological information cannot be continuously communicated from the biological information monitors to the system software due to communication failure or other reasons,
(b) information about the syringe pumps cannot be continuously communicated to the system software or information about the administered dose of the anesthetic drugs cannot be communicated due to communication failure or other reasons,
(c) malfunctions of Robotic Anesthesia System or the PC occurs, or
(d) the drug cannot be administered due to malfunctions of a syringe pump or other reasons, or the biological information cannot be measured due to malfunctions of a biological information monitor or other reasons.

In the cases of (a) to (c), an alarm message or a message indicating abnormality is displayed on Robotic Anesthesia System. Where the system software does not return to the appropriate automatic mode even if the operation is performed according to the message, the anesthesiologist stops the automated control of anesthesia by Robotic Anesthesia System and manually override the operation of the syringe pumps. For the case of (d), the alarm from the syringe pump or the biological information monitor with malfunctions should be responded. In this case, the anesthesiologist should stop the automated control of anesthesia by Robotic Anesthesia System and manually override the operation of the syringe pumps because the information required for automated control of anesthesia cannot be communicated from the syringe pump or the biological information monitor to the system software. If Robotic Anesthesia System fails, the anesthesiologist should leave Robotic Anesthesia System as it is and switch to the manual operation of the syringe pumps. Even if Robotic Anesthesia System becomes unusable, the information necessary for anesthesia management can be checked with the biological information monitors or syringe pumps.

PMDA's view:
It is important to ensure that the anesthesiologist can manually override the operation of the syringe pumps immediately when any problem such as difficulty in control occurs with Robotic Anesthesia System. That is, anesthesiologists must be able to recognize that the condition is unmanageable, understand information such as the dose controlled by Robotic Anesthesia System, and switch to

manual mode appropriately. To this end, anesthesiologists should become familiar with the operating principle, method of use, method of troubleshooting, and other aspects of Robotic Anesthesia System, and the development of proper-use guidelines including user training is essential.

Based on the above, PMDA concluded that there is no particular safety problem with the use of the automated control of anesthesia by Robotic Anesthesia System.

6.B.(4) Concomitant drugs

The applicant's explanation:
Generic drugs not used in the clinical study can be used with Robotic Anesthesia System if their non-proprietary names and concentrations are the same as those shown in Table 15.

Table 15. Drugs concomitantly used with Robotic Anesthesia System as anticipated by the applicant

Non-proprietary name	Concentration
Propofol	10 mg/mL
Remifentanil hydrochloride	0.1 mg/mL
Rocuronium bromide	10 mg/mL

PMDA asked the applicant to explain the types of anesthetics (propofol, remifentanil, and rocuronium) used in the Japanese clinical study and the efficacy of Robotic Anesthesia System for each drug.

The applicant's response:
Propofol used in the Japanese clinical study was "1% Diprivan Injection-Kit" (the brand-name drug) only. For remifentanil, all drugs intended to be used at this point in time were used (Table 16). For rocuronium, the brand-name drug and 1 of the 3 generic drugs approved at this point in time were used (Table 17). There was no difference in efficacy between the brand-name and generic drugs of remifentanil and rocuronium in the Japanese clinical study (Tables 18 and 19).

Although the Japanese clinical study did not cover all generic drugs that can be used with Robotic Anesthesia System, these generic drugs have the same indications and dosage regimen as the brand-name drugs. If the generic drugs are used for anesthesia, the results will be comparable to the efficacy and safety results in the Japanese clinical study. Given this situation, specifying the non-proprietary names and concentrations of drugs that can be used with Robotic Anesthesia System is reasonable.

Table 16. Remifentanil used in the Japanese clinical study

Brand-name drug	Ultiva Intravenous 2 mg (Table 18) Ultiva Intravenous 5 mg (Table 18)
Generic drug	Remifentanil for Intravenous Injection 2 mg "Daiichi Sankyo" (Approval number, 22800AMX00090) (Table 18) Remifentanil for Intravenous Injection 5 mg "Daiichi Sankyo" (Approval number, 22800AMX00091) (Table 18)

Table 17. Rocuronium used in the Japanese clinical study

Brand-name drug	Eslax Intravenous 25 mg/2.5 mL (Table 19) Eslax Intravenous 50 mg/5.0 mL (Table 19)
Generic drug	Rocuronium Bromide Intravenous Solution 25 mg/2.5 mL "Maruishi" (Approval number, 22800AMX00533) (Table 19) Rocuronium Bromide Intravenous Solution 50 mg/5.0 mL "Maruishi" (Approval number, 22800AMX00534) (Table 19)

Table 18. Percentage of time in which analgesia was appropriately maintained for each type of remifentanil (%)

	Overall (N = 59)	Ultiva (N = [redacted])	Generic drug (N = [redacted])
Mean	99.56	[redacted]	[redacted]
Standard deviation	1.86	[redacted]	[redacted]
Minimum	88.1	[redacted]	[redacted]
Median	100.00	[redacted]	[redacted]
Maximum	100.0	[redacted]	[redacted]

Table 19. Percentage of time in which muscle relaxation was appropriately maintained for each type of rocuronium (%)

	Overall (N = 59)	Eslax (N = [redacted])	Generic drug (N = [redacted])
Mean	90.84	[redacted]	[redacted]
Standard deviation	12.60	[redacted]	[redacted]
Minimum	29.2	[redacted]	[redacted]
Median	94.78	[redacted]	[redacted]
Maximum	100.0	[redacted]	[redacted]

PMDA's view:

Robotic Anesthesia System controls the doses in the range of dosage regimen of the brand-name drugs of propofol, remifentanil, and rocuronium. In light of the principle of the automated control of anesthesia by Robotic Anesthesia System, the dose of generic drugs with the same dosage form, ingredient and strength (concentration), indications, and dosage regimen as the brand-name drugs is expected to be automatically controlled by Robotic Anesthesia System similarly to the brand-name drugs. However, there is no evidence for such use. In addition, while the generic drugs currently approved have the same dosage form, ingredient and strength (concentration), indications, and dosage regimen as the brand-name drugs, those of generic drugs newly approved in the future are unknown. Therefore, PMDA instructed the applicant to (a) inform healthcare professionals that there is no evidence showing that generic drugs not used in the Japanese clinical study can be automatically controlled by Robotic Anesthesia System and to provide relevant precautions through the Information on Precautions, etc. so that generic drugs are used with careful monitoring of the patient's condition, and (b) specify that the drugs that can be used with Robotic Anesthesia System are the brand-name drugs of propofol, remifentanil, and rocuronium as well as their generic drugs with the same non-proprietary name, dosage form, ingredient and strength (concentration), indications, and dosage regimen. The applicant responded to these instructions.

Based on the above discussion, PMDA decided to accept the use of generic drugs including those not used in the Japanese clinical study.

6.B.(5) Indications

The applicant's explanation:

Robotic Anesthesia System is indicated for use in patients eligible for the drugs (propofol, remifentanil, and rocuronium). The eligible patients include patients who were excluded from the Japanese clinical study, i.e., patients with ASA-PS ≥4, patients undergoing therapeutic hypothermia during surgery, patients undergoing cardiovascular surgery, patients undergoing nerve block during surgery, and pregnant or nursing women.

PMDA's view on whether patients excluded from the clinical study can be included in the patients for whom Robotic Anesthesia System is indicated is described in 1) to 6) below. PMDA instructed the applicant to include the following statement in the Intended Use or Indications section: Robotic Anesthesia System is not indicated for patients with ASA-PS ≥4, patients undergoing therapeutic hypothermia during surgery, patients undergoing cardiovascular surgery, and pregnant women. The applicant responded to the instruction.

Based on the above, PMDA has concluded that there is no particular problem with the indication of Robotic Anesthesia System.

1) Patients with ASA-PS ≥4

In light of the operating principle of Robotic Anesthesia System, it is highly likely that the administration of a sedative, an analgesic and a muscle relaxant can be controlled regardless of the ASA-PS classification. On the other hand, only 2 subjects with ASA-PS 3 were included in the Robotic Anesthesia System group in the Japanese clinical study. Most of the efficacy and safety results of Robotic Anesthesia System were obtained from patients with ASA-PS ≤2. Considering that patients with ASA-PS ≥4 have unstable general conditions and often require unusual management for administration of anesthetics, it is difficult to extrapolate the safety results of Robotic Anesthesia System to patients with ASA-PS ≥4.

2) Patients who undergo therapeutic hypothermia during surgery

Since the deep body temperature of a patient undergoing therapeutic hypothermia is maintained at approximately 34°C, a decrease in the rate of drug metabolism, etc. is assumed in the patient, who requires unusual management for administration of anesthetics. It is difficult to extrapolate the efficacy and safety results of Robotic Anesthesia System in the Japanese clinical study to patients undergoing therapeutic hypothermia during surgery.

3) Patients who undergo cardiovascular surgery

Patients undergoing cardiovascular surgery are expected to be hemodynamically unstable during surgery. For this reason, such patients require unusual management for administration of anesthetics. It is difficult to extrapolate the efficacy and safety results of Robotic Anesthesia System in the Japanese clinical study to the patients undergoing cardiovascular surgery.

4) Pregnant women

Since sensitivity to anesthetics increases during pregnancy, the adjustment of anesthetics is required in pregnant women. In general, anesthesia management for pregnant women is different from usual because it is, for example, based on non-pregnant body weight. Because the management method using Robotic Anesthesia System for pregnant women has been unclarified, it is difficult to extrapolate the efficacy and safety results of Robotic Anesthesia System in the Japanese clinical study to pregnant women.

5) Patients who undergo nerve block during surgery

Patients undergoing nerve block were excluded from the Japanese clinical study because the appropriate levels of sedation, analgesia, and muscle relaxation had to be evaluated after administration of propofol, remifentanil, and rocuronium. However, anesthesia management during surgery for patients undergoing nerve block is not separately performed in clinical practice. It is possible to extrapolate the efficacy and safety results of Robotic Anesthesia System in the Japanese clinical study to patients undergoing nerve block during surgery, in light of the operating principle of Robotic Anesthesia System. On the condition that the Information on Precautions, etc. includes the precautionary statement that patients undergoing nerve block during surgery were not included in the Japanese clinical study, such patients can be subjected to anesthesia using Robotic Anesthesia System.

6) Nursing women

The effect of anesthetics on breastfeeding should be taken into consideration in nursing women. However, intraoperative anesthesia management in nursing women requiring general anesthesia is not substantially different from that for patients who are not breastfeeding. For this reason, it is possible to extrapolate the efficacy and safety results of Robotic Anesthesia System in the Japanese clinical study to nursing women. On the condition that the Information on Precautions, etc. includes the precautionary statement that nursing women were not included in the Japanese clinical study, nursing women can be subjected to anesthesia using Robotic Anesthesia System.

6.B.(6) Post-marketing safety measures including proper use such as user training

As described in Section “6.B.(3) Safety of Robotic Anesthesia System,” anesthesiologists should become familiar with the operating principle, method of use, method of troubleshooting, and other aspects of Robotic Anesthesia System, and the development of proper-use guidelines such as user training is essential.

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 considered that the product would not be subject to the use-results survey, and thus did not submit documents related to the post-marketing surveillance plan, etc.

7.B Outline of the review conducted by PMDA

PMDA' view:

Although there were no particular problems with the safety results of Robotic Anesthesia System in the Japanese clinical study, the types of surgical procedures used in the Robotic Anesthesia System group in the study were limited, most of the surgeries required a short operation time with the mean of 151.1 minutes and the median of 135 minutes, and only 2 subjects with ASA-PS 3 were included in the Robotic Anesthesia System group. Given these points, information on the safety of Robotic Anesthesia System used in clinical settings should be collected in a use-results survey to verify whether the results are not substantially different from the clinical study results. PMDA requested the applicant to submit data for the plan of post-marketing surveillance, etc.

The applicant submitted the summary of the basic plan of a use-results survey (Table 20).

Table 20. Outline of use-results survey plan (draft)

Objective	To investigate the safety of Robotic Anesthesia System used for general anesthesia with propofol, remifentanil, and rocuronium in clinical practice.
Sample size	150 patients (75 patients with ASA-PS 1 or 2 and 75 patients with ASA-PS 3)
Number of study sites	2 study sites
Survey period	4 years and 8 months after the date of marketing approval (preparation period, 1 year and 5 months; enrollment period, 3 years; follow-up period, -; analysis period, 3 months)
Survey items	Adverse events, malfunctions of Robotic Anesthesia System (key survey item, adverse events in patients with ASA-PS 3)

7.B.(1) Rationale for sample size

In the Japanese clinical study, adverse events for which a causal relationship to Robotic Anesthesia System could not be ruled out occurred in 3 of 60 subjects (5.0%). Assuming that adverse events occur at a similar frequency in clinical practice, 59 patients are required to detect at least 1 patient with a probability of at least 95%. On the assumption that a dropout rate is approximately 20% in this survey, the number of patients with ASA-PS 3 was 75, and the number of patients with ASA-PS 1 or 2 was 75.

7.B.(2) Survey items

Characteristics of patients (sex, date of birth, height, body weight, ASA-PS, complications, disease subject to surgery, and surgical procedure) and safety information (adverse events reported in patients, adverse events reported in healthcare professionals who use the system software, and malfunctions of Robotic Anesthesia System) were selected.

PMDA accepted the use-results survey plan for Robotic Anesthesia System.

8. Documents Related to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as attachment in accordance with the Notification "Application for Marketing Approval of Medical Device" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Section "6.B Outline of the review conducted by PMDA," PMDA concluded that there was no particular problem with the proposed Information on Precautions, etc., provided that the applicant would advise necessary precautions.

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 new medical device application data were subjected to a document-based compliance 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 documents submitted.

PMDA's conclusion concerning the results of the on-site GCP inspection

The new medical device application data were subjected to an on-site GCP, 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, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

Robotic Anesthesia System is a software program designed to control the doses of propofol, remifentanil, and rocuronium by controlling the connected syringe pumps during surgery in general anesthesia using intravenous anesthetics under the supervision of an anesthesiologist. The Japanese clinical study evaluated the efficacy and safety of the automated control of anesthesia by Robotic Anesthesia System in patients aged ≥20 years who were to undergo general anesthesia with propofol, remifentanil, and rocuronium. The key issues in evaluating Robotic Anesthesia System are (1) the efficacy of Robotic Anesthesia System and (2) the safety of Robotic Anesthesia System and post-marketing safety measures. The conclusion of PMDA, taking also account of comments raised in the Expert Discussion, is shown below.

(1) Efficacy of Robotic Anesthesia System

For the efficacy of Robotic Anesthesia System, the "percentage of time in which all of sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time," the primary endpoint, was 87.21% ± 12.79% in the Robotic Anesthesia System group and 65.19% ± 20.16% in the control group, demonstrating the non-inferiority of Robotic Anesthesia System to the control ($P < 0.001$). For the secondary endpoints, the percentage of time in which sedation, analgesia, and muscle relaxation were appropriately maintained during the operation time, and other measures were evaluated. The results demonstrated the non-inferiority of Robotic Anesthesia System to the control ($P < 0.001$). In addition, the evaluation of the time from the start of anesthesia to skin incision and the time from the end of anesthesia to eye-opening in response to verbal stimuli showed similar results between the Robotic Anesthesia System group and the control group. These results are considered to support the efficacy of Robotic Anesthesia System.

(2) Safety of Robotic Anesthesia System and post-marketing measures

The safety data of Robotic Anesthesia System were analyzed. No serious adverse events for which a causal relationship to Robotic Anesthesia System could not be ruled out or malfunctions of Robotic Anesthesia System were reported. However, clinical safety information has been insufficiently collected in the Japanese clinical study, given that the types of surgical procedures used for Robotic Anesthesia System in the Japanese clinical study was limited in light of surgical procedures used in clinical settings, that most of the surgeries required a relatively short operation time, and that only 2 subjects with ASA-PS 3 were included in the Robotic Anesthesia System group. Therefore, post-marketing information on the incidence of adverse events and malfunctions should be collected continuously through the use-results survey to take risk mitigation measures. In addition, it is important to ensure that the anesthesiologist can manually override the operation of syringe pumps immediately in the event of any problem such as difficulty in anesthesia management with Robotic Anesthesia System. That is, anesthesiologists must be able to recognize that the condition is unmanageable, understand information such as the dose controlled by Robotic Anesthesia System, and switch to manual mode appropriately. To this end, anesthesiologists should become familiar with the operating principle, method of use, method of troubleshooting, and other aspects of Robotic Anesthesia System, and the development of proper-use guidelines including user training is essential. PMDA has been concluded that there is no particular safety problem in the automated control of anesthesia by Robotic Anesthesia System as long as these measures are taken.

Given that compliance with the proper-use guidelines prepared by related academic societies including the above contents is necessary for the safe use of Robotic Anesthesia System, these requirements should be included in the approval condition.

The use-results survey period should be 4 years and 8 months (preparation period, 1 year and 5 months; enrollment period, 3 years; follow-up period, -; analysis period, 3 months). Information on the safety of Robotic Anesthesia System used in clinical settings should be collected to verify whether the results are not substantially different from the clinical study results.

As a result of the above review, PMDA has concluded that Robotic Anesthesia System may be approved after modifying the intended use as shown below, with the following approval conditions.

Intended Use

This software is intended to assist in the administration of total intravenous anesthesia by automatically calculating the doses of propofol, remifentanil hydrochloride, and rocuronium bromide to be delivered to adult patients (excluding patients with ASA-PS ≥4, patients undergoing therapeutic hypothermia during surgery, patients undergoing cardiovascular surgery, and pregnant patients) under total intravenous anesthesia, and by controlling the connected syringe pumps.

Approval Conditions

The applicant is required to take measures to ensure that anesthesiologists with sufficient knowledge and experience related to the indication of the product use the product appropriately in accordance with the proper-use guidelines prepared by related academic societies, after obtaining a full understanding of the principle of the product, anesthesia management using the product, emergency response, etc. by attending relevant seminars or through other means.

The product is not classified as a biological product or a specified biological product. The product should be designated as a medical device that is subjected to a use-results survey. The use-results survey period should be 4 years and 8 months.

PMDA has concluded that this application should be deliberated at the Subcommittee on Software as a Medical Device.

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