SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Pulmonary valve, prosthesis, percutaneously delivered
Device Trade Name:	Edwards SAPIEN 3 Transcatheter Heart Valve System with Edwards Commander Delivery System
Device Procode:	NPV
Applicant Name and Address:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P200015
Date of FDA Notice of Approval:	August 31, 2020

II. INDICATIONS FOR USE

The Edwards SAPIEN 3 Transcatheter Heart Valve (THV) System with Edwards Commander Delivery System is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic valve in the pulmonic position with ≥ moderate regurgitation and/or a mean RVOT gradient of ≥ 35 mmHg.

III. CONTRAINDICATIONS

The Edwards SAPIEN 3 THV System with Edwards Commander Delivery System is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Edwards SAPIEN 3 THV System with Edwards Commander Delivery System labeling.

V. DEVICE DESCRIPTION

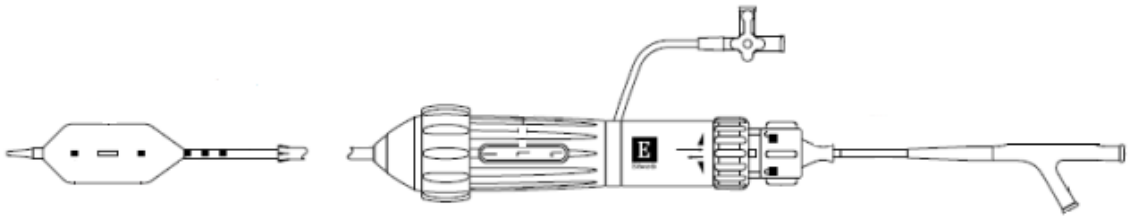
The Edwards SAPIEN 3 THV, as shown in Figure 1, is comprised of a balloon-expandable,

radiopaque, cobalt-chromium (MP35N) frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET external sealing skirt for reduction of paravalvular leakage (PVL). The leaflets are treated according to the Edwards ThermaFix process.

Figure 1: SAPIEN 3 Transcatheter Heart Valve

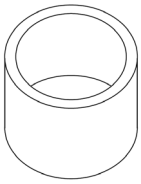
The Edwards Commander Delivery System, as shown in Figure 2, includes a handle that provides a flex wheel for articulation of the flex catheter, a tapered tip at the distal end of the delivery system, a balloon catheter for deployment of the THV, and radiopaque markers.

Figure 2: Edwards Commander Delivery System



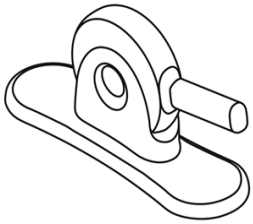
The Qualcrimp crimping accessory, as shown in Figure 3, is a non-patient contacting device that is placed around the THV to protect the leaflets during the crimping process. It is manufactured of tubular polyester polyurethane foam and laminated cylindrically on both the inner and outer surfaces with a polyether urethane material.

Figure 3: Qualcrimp Crimping Accessory



The Edwards Crimper, as shown in Figure 4, is comprised of various molded plastic components which compress the valve to a controlled aperture. The aperture is created by rotating the handle until it abuts the crimp stopper. The Edwards Crimper is used with a Crimp Stopper to correctly crimp the THV.

Figure 4: Edwards Crimper



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of a dysfunctional RVOT conduit or surgical bioprosthetic valve in the pulmonic position, including balloon valvuloplasty; surgical replacement with a homograft, a valved conduit, or another bioprosthetic valve; and implantation of another approved transcatheter pulmonary valve. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Edwards SAPIEN 3 THV System with Edwards Commander Delivery System has not been marketed in the United States or any foreign country for the indication of treatment of a dysfunctional RVOT conduit and bioprosthetic valve in the pulmonic position.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Death
- Stroke/transient ischemic attack
- Respiratory insufficiency or respiratory failure
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium or valvular structures including rupture of the RVOT that may require intervention
- Pericardial effusion/cardiac tamponade
- Embolic event: air, calcific material, thrombus, device fragments
- Infection including incisional site infection, septicemia and endocarditis
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system injury
- Arrhythmia
- Arteriovenous (AV) fistula
- Systemic or peripheral nerve injury
- Systemic or peripheral ischemia

- Pulmonary edema
- Pneumothorax
- Pleural effusion
- Atelectasis
- Blood loss requiring transfusion
- Anemia
- Radiation injury
- Electrolyte imbalance
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials
- Hematoma or ecchymosis
- Syncope
- Pain
- Exercise intolerance or weakness
- Inflammation
- Angina
- Fever
- Cardiac arrest
- Cardiogenic shock
- Cardiac failure
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Injury to tricuspid valve
- Device embolization requiring intervention
- Device acute migration or malposition requiring intervention
- Endocarditis
- Hemolysis / hemolytic anemia
- THV dysfunction resulting in pulmonary valve symptoms
- Mechanical failure of delivery system, and/or accessories
- Emergent and non-emergent re-intervention
- Dyspnea

For the specific adverse events that occurred in the real-world clinical practice, please see Section X.

IX. SUMMARY OF PRECLINICAL STUDIES

A summary of previously reported preclinical studies on the Edwards SAPIEN 3 THV System with Edwards Commander Delivery System can be found in the SSED for PMA P140031 (https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031B.pdf) for the aortic indication. The following additional preclinical studies were performed to support the pulmonic indication.

A. Laboratory Studies

Design Verification

Edwards SAPIEN 3 THV

Design verification studies were performed to evaluate the hydrodynamic performance and sizing of the Edwards SAPIEN 3 pulmonic THV-in-surgical valve configuration, as summarized in Table 1.

Table 1: SAPIEN 3 THV Design Verification Studies

Test / Standard	Purpose/Objective	Results
Hydrodynamic testing: SAPIEN 3 THV-in-surgical valve ISO 5840-3:2013	Pulsatile hydrodynamic testing of SAPIEN 3 pulmonic THV-in-surgical valve configuration.	Pass
Pulmonic THV-in-surgical valve sizing	Assessment of SAPIEN 3 positioning for pulmonic THV-in-surgical valve to develop positioning guidance.	Completed

Edwards Commander Delivery System

A design verification study was performed to evaluate the compatibility of the Edwards SAPIEN 3 THV System with Edwards Commander Delivery System and the GORE DrySeal Flex Introducer Sheath, as summarized in Table 2.

Table 2: Edwards Commander Delivery System Design Verification Study

Test	Purpose/Objective	Results
Compatibility of the SAPIEN 3 THV System with the GORE DrySeal Sheath	Evaluation of the compatibility of the SAPIEN 3 THV and Commander Delivery System with the GORE DrySeal Flex Introducer Sheath	Pass

Design Validation

A design validation study was conducted to demonstrate that the SAPIEN 3 THV System with Edwards Commander Delivery System used with the Edwards eSheath or the GORE DrySeal Sheath meets the users' needs, as summarized in Table 3.

Table 3: SAPIEN 3 THV System Design Validation Study

Test	Purpose/Objective	Results
SAPIEN 3 THV System used with eSheath or GORE DrySeal Sheath	Confirm that the users' needs are met for the SAPIEN 3 THV System used with the eSheath or GORE DrySeal Sheath.	Pass

X. SUMMARY OF CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Edwards SAPIEN 3 THV System with Edwards Commander Delivery System in patients with a dysfunctional ROVT conduit or bioprosthetic valve in the pulmonic position under IDE G150220 (entitled the "COMPASSION S3" study). The data from this study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The COMPASSION S3 study was a single-arm, prospective, multicenter study. Patients were enrolled between July 2016 and July 2018 at 11 investigational sites in the U.S. The database for this PMA reflected data collected through November 4, 2019.

The COMPASSION S3 study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the study. An independent echocardiographic core laboratory was used for standardized assessment of echocardiograms.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the COMPASSION S3 study was limited to patients who met the following inclusion criteria:

   - Weight ≥ 20 kg (44 lbs.)
   - Dysfunctional RVOT conduit or previously implanted valve in the pulmonic position with a clinical indication for intervention and with a landing zone diameter ≥ 16.5 mm and ≤ 29 mm immediately prior to study device insertion as per the Instructions for Use.
   - Subject presents with at least moderate pulmonary regurgitation (PR) and/or mean RVOT gradient ≥ 35 mmHg.
   - The subject or subject's legally authorized representative (LAR) has been informed of the nature of the study, agrees to its provisions and has provided written informed consent.

   Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

   - Active infection requiring current antibiotic therapy (if temporary illness, subject may be a candidate 2 weeks after discontinuation of antibiotics)
   - History of or active endocarditis (active treatment with antibiotics) within the past 180 days

- Leukopenia (white blood cells [WBC]<2000 cells/μL), anemia (hemoglobin [Hgb] < 7 g/dL), thrombocytopenia (platelets < 50,000 cells/μL) or any known blood clotting disorder
- Inappropriate anatomy for femoral introduction and delivery of the SAPIEN 3 THV
- Need for concomitant atrial septal defect (ASD) or ventricular septal defect (VSD) closure or other concomitant interventional procedures other than pulmonary artery or branch pulmonary artery stenting or angioplasty
- Angiographic evidence of coronary artery compression that would result from transcatheter pulmonic valve implantation (TPVI)
- Emergency interventional/surgical procedures within 30 days prior to the TPVI procedure.
- Any planned surgical, percutaneous coronary or peripheral procedure to be performed within the 30-day follow-up from the TPVI procedure.
- History of or current intravenous drug use
- Major or progressive non-cardiac disease resulting in a life expectancy of <1 year
- Known hypersensitivity to aspirin or heparin and cannot be treated with other antiplatelet and/or antithrombotic medications
- Known hypersensitivity to cobalt-chromium, nickel or contrast media that cannot be adequately premedicated
- Currently participating in an investigational drug or another device study. [Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational devices.]
- Positive urine or serum pregnancy test in female subjects of child-bearing potential

2. Follow-up Schedule

Follow-up time points included discharge, 30 days, 6 months, and 1 year post index procedure, and will continue annually thereafter to 5 years post procedure. Preoperative and post-operative assessments included physical assessment and medical history, laboratory measurements, imaging tests, and exercise testing. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

The primary endpoint was THV dysfunction at 1 year defined as a non-hierarchical composite of:

- RVOT reintervention
- Moderate or greater total PR via transthoracic echocardiogram (TTE; as assessed by echocardiographic core laboratory)
- Mean RVOT gradient > 40 mmHg via TTE (as assessed by echocardiographic core laboratory)

A performance goal of 25% was pre-specified for the primary endpoint. The hypothesis for the primary endpoint was as follows:

$$H_0: \pi_{COMPASSION} \geq 25\%$$
$$H_A: \pi_{COMPASSION} < 25\%$$

where $\pi_{COMPASSION}$ represented the composite event rate at 1 year. If the upper 95% confidence limit for the composite event was less than 25%, the performance goal would be met. The hypothesis was tested at a one-sided significance level of 0.025.

The secondary effectiveness endpoints included the following:

- Device success, defined as a composite of single THV implanted in the desired location, right ventricle to pulmonary artery (RV-PA) peak-to-peak gradient < 35 mmHg post-implantation, less than moderate PR by discharge TTE (or earliest evaluable TTE), and free of explant at 24 hours post-implantation
- THV hemodynamic function at 6 months (including mean RVOT gradient via TTE, paravalvular and total PR via TTE, and RVOT reintervention)
- New York Heart Association (NYHA) functional class

The secondary safety endpoints included the following:

- Freedom from coronary artery compression requiring intervention at 30 days
- Freedom from major vascular complications at 30 days
- Freedom from life-threatening or disabling bleeding at 30 days
- Freedom from THV frame fracture at 6 months
- Freedom from device-related endocarditis at 1 year
- Freedom from death (all cause, device- and procedure-related) at 1 year

B. Accountability of the PMA Main Cohort

At the time of database lock, a total of 58 subjects were enrolled in the study, including 38 with a dysfunctional RVOT and 20 with a dysfunctional bioprosthetic valve in the pulmonic position.

There were 3 different analysis populations defined in the protocol: All Treated (AT), Attempted Implant (AI), and Valve Implant (VI), as summarized in Table 4.

Table 4: Analysis Populations

Analysis Population	Definition	Number of Patients
All Treated	All subjects who signed informed consent, passed screening and for whom the procedure was begun (defined as the time of vascular access – incision or puncture).	58
Attempted Implant	All AT subjects who had an attempted implant of the study valve (introducer sheath for vascular delivery of the SAPIEN 3 THV was inserted into the subject).	56

Valve Implant	All AI patients who received and retained the intended valve upon leaving the catheterization laboratory/hybrid suite.	56

Study visit compliance is summarized in Table 5. Two subjects exited the study prior to the 1-year visit.

Table 5: Study Visit Compliance

	AT Population (N=58)		
	30 Days	**6 Months**	**1 Year**
Ineligible*	2	2	2
Eligible	56	56	56
Visit performed	55 (98.2%)	54 (96.4%)	52 (92.9%)

*Ineligible subjects included those who exited the study prior to the visit.

C. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a transcatheter pulmonary valve study performed in the U.S., as shown in Table 6.

Table 6: Demographics and Baseline Characteristics (AT Population)

Variable	Summary Statistics* (N=58)
Age (years)	31.8 ± 13.2 (58)
<12 years (child)	8.6% (5/58)
12 - 21 years (adolescent)	13.8% (8/58)
≥22 years (adult)	77.6% (45/58)
Gender	
Male	69.0% (40/58)
Weight (kg)	74.1 ± 21.2 (58)
NYHA class	
Class I	15.8% (9/57)
Class II	73.7% (42/57)
Class III	10.5% (6/57)
Class IV	0.0% (0/57)
NYHA class grouped	
Class I/II	89.5% (51/57)
Class III/IV	10.5% (6/57)

Variable	Summary Statistics* (N=58)
Primary indication	
Pulmonary stenosis only	12.3% (7/57)
Pulmonary regurgitation only	19.3% (11/57)
Both	68.4% (39/57)
Original CHD diagnosis	
Aortic valve disease resulting in Ross procedure	21.1% (12/57)
Atrial septal defect	17.2% (10/58)
Coarctation of the aorta	1.7% (1/58)
Double outlet right ventricle	5.2% (3/58)
Pulmonary atresia	17.2% (10/58)
Pulmonary valve stenosis	50.0% (29/58)
Tetralogy of Fallot	55.2% (32/58)
Transposition of the great arteries	6.9% (4/58)
Truncus arteriosus	5.2% (3/58)
Ventricular septal defect	34.5% (20/58)
Other	32.8% (19/58)
Most recent RVOT/PV repair/replacement	
Homograft	50.0% (29/58)
Biological valved conduit	13.8% (8/58)
Synthetic valved conduit	1.7% (1/58)
Surgical heart valve	34.5% (20/58)

*Continuous measures - Mean ± SD (Total no.); categorical measures - % (no./Total no.)

The distribution of prior cardiac interventions in the AT population stratified by patient age is shown in Table 7. The minimum and maximum diameters of the landing zone stratified by prior cardiac intervention and patient age are provided in Table 8.

Table 7: Prior Cardiac Interventions by Age Group (AT Population)

Variable	Summary Statistics*		
	<12 Years (N= 5)	12-21 Years (N= 8)	≥22 Years (N= 45)
Most recent RVOT/PV repair/replacement			
Homograft	60.0% (3/5)	37.5% (3/8)	51.1% (23/45)
Biological valved conduit	20.0% (1/5)	50.0% (4/8)	6.7% (3/45)
Synthetic valved conduit	0.0% (0/5)	0.0% (0/8)	2.2% (1/45)
Surgical heart valve	20.0% (1/5)	12.5% (1/8)	40.0% (18/45)

*Categorical measures - % (No. / Total no.).

Table 8: Landing Zone Diameters by Prior Cardiac Interventions and Patient Age (AT Population)

Most Recent RVOT Repair / Replacement	Summary Statistics*					
	<12 Years (N=5)		12-21 Years (N=8)		≥22 Years (N=45)	
	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)
All Subjects	17.8±1.8 (5/5)	19.3±0.8 (5/5)	21.9±4.7 (6/8)	24.3±0.9 (6/8)	20.4±3.1 (40/45)	23.0±4.3 (41/45)
Homograft	17.4±2.4 (3/5)	19.2±1.0 (3/5)	18.4±7.9 (2/8)	24.2±0.2 (3/8)	20.1±3.5 (22/45)	23.0±5.4 (23/45)
Biological valved conduit	19.0±NA (1/5)	20.0±NA (1/5)	22.8±1.8 (3/8)	23.5±0.2 (2/8)	18.0±2.6 (3/45)	21.0±1.0 (3/45)
Synthetic valved conduit	NA	NA	NA	NA	18.7±NA (1/45)	19.7±NA (1/45)
Surgical heart valve	18.0±NA (1/5)	19.0±NA (1/5)	25.9±NA (1/8)	25.9±NA (1/8)	21.6±2.0 (14/45)	23.7±2.3 (14/45)

*Continuous measures - Mean ± SD (No./Total no.)

D. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 9. THV dysfunction at 1 year was 4.3% (CI: 0.5% to 14.5%). Since the upper limit of the 95% confidence interval for the primary endpoint event rate was < 25%, the endpoint was met.

Table 9: Primary Endpoint: THV Dysfunction at 1 year (VI Population)

Endpoint	Summary Statistics* (N=56)	95% Confidence Interval	Less than the pre-specified performance goal (25%)?
THV dysfunction	4.3% (2/47)	(0.5%, 14.5%)	Yes
RVOT reintervention†	0.0% (0/56)	(0.0%, 6.4%)	
Moderate or greater PR	2.1% (1/47)	(0.1%, 11.3%)	
Mean RVOT gradient >40 mmHg	2.1% (1/48)	(0.1%, 11.1%)	

*Summary statistics: Categorical measures - % (no./total no.)
†Includes reintervention for both RVOT conduit and THV

2. Secondary Safety Endpoints

The results of the secondary safety endpoints as adjudicated by the CEC are summarized in Table 10.

Table 10: Summary of Secondary Safety Endpoint Results (AT Population)

Freedom from Adverse Events	Summary Statistics*
30-day endpoints (at risk† =57)	
Coronary artery compression requiring intervention post-implantation	100.0% (0, 0)
Major vascular complications	100.0% (0, 0)
Life-threatening or disabling bleeding	100.0% (0, 0)
6-month endpoint (at risk =55)	
THV frame fracture (site-reported)	100.0% (0, 0)
1-year endpoints (at risk =51)	
All-cause death	100.0% (0, 0)
Procedure- or device-related death	100.0% (0, 0)
Device related endocarditis	100.0% (0, 0)

*Kaplan-Meier estimate (No. events, No. patients with event)
†At risk numbers reflect the number of subjects on study at the end of the interval.

3. Secondary Effectiveness Endpoints

Device Success

Device success was achieved in 98.1% of the subjects, as shown in Table 11.

Table 11: Device Success (AI Population)

Endpoint	Summary Statistics* (N=56)
Device success	98.1% (53/54)
Single THV implanted in the desired location	98.2% (55/56)
RV-PA peak-to-peak gradient < 35 mmHg post implantation	100.0% (56/56)
Less than moderate PR by discharge TTE (or earliest evaluable TTE)	100.0% (54/54)
Free of explant at 24 hours post implantation	100.0% (56/56)

*Categorical measures - % (no./total no.)

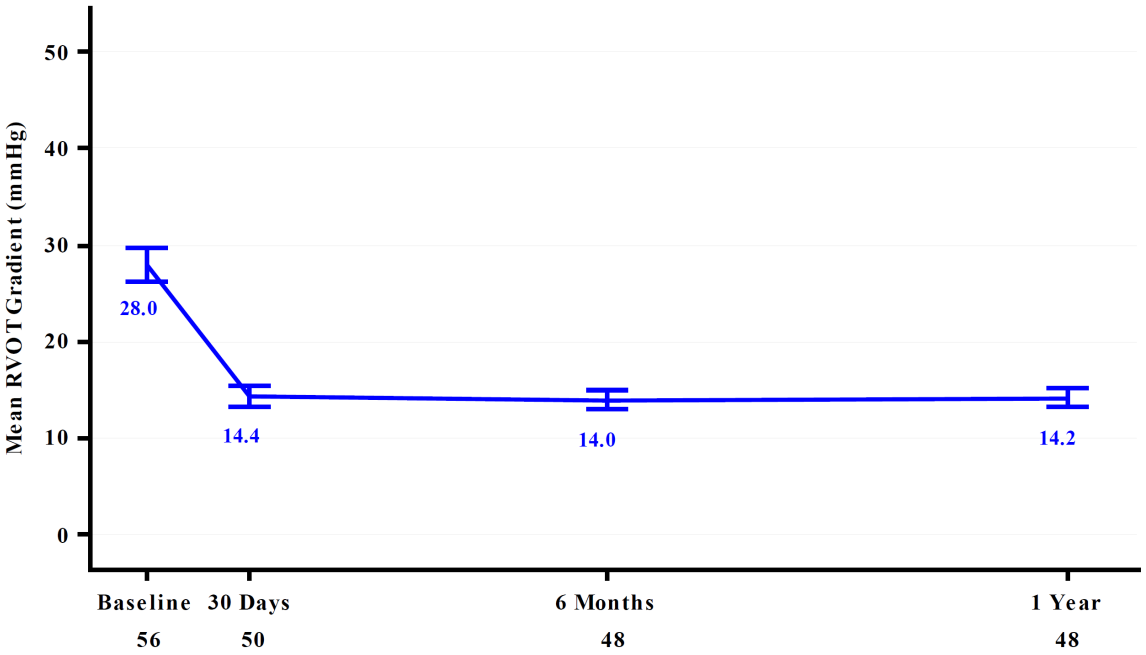
RVOT Reintervention

No subject had RVOT reintervention within 1 year of the valve implant procedure.

THV Hemodynamic Function

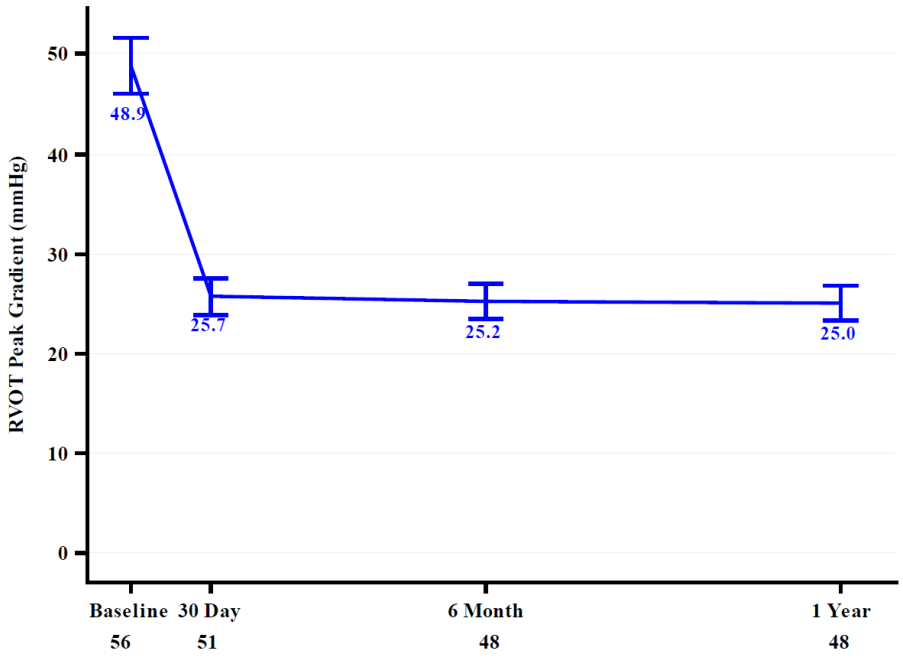
The mean RVOT gradient, peak RVOT gradient, peak RVOT gradient stratified by landing zone type, total PR and paravalvular regurgitation results at 1 year are shown in Figure 5 through Figure 9, respectively. The decrease in gradient was sustained through 1 year. The proportion of patients with total PR ≥ moderate was 0.0% at 30 days and 2.1% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.0% at 30 days and 1 year.

Figure 5: Mean RVOT Gradient (VI Population)



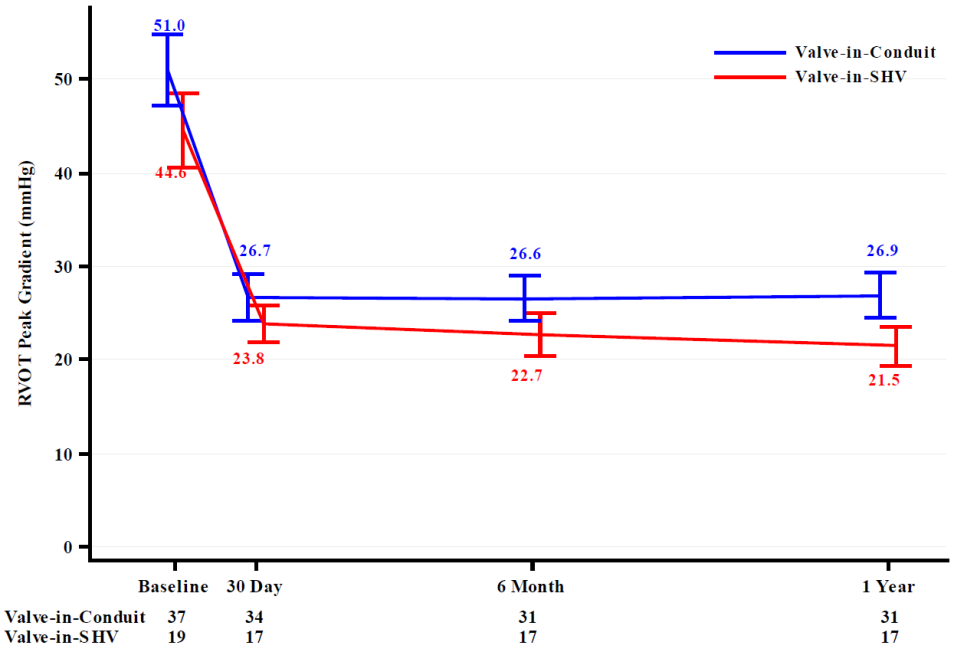
Note: Line plot with mean and standard error. The total number of subjects at each visit time point only counted the subjects with valid values.

Figure 6: Peak RVOT Gradient (VI Population)



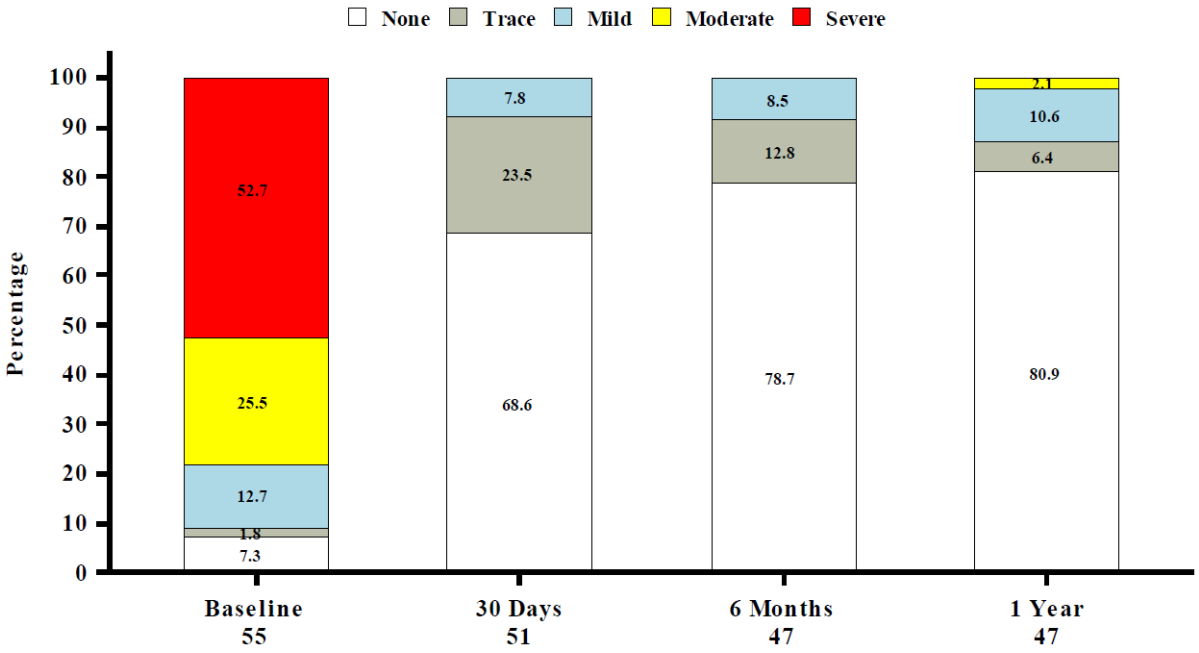
Note: Line plot with mean and standard error. The total number of subjects at each visit time point only counted the subjects with valid values.

Figure 7: RVOT Peak Gradient by Landing Zone Type (VI Population)



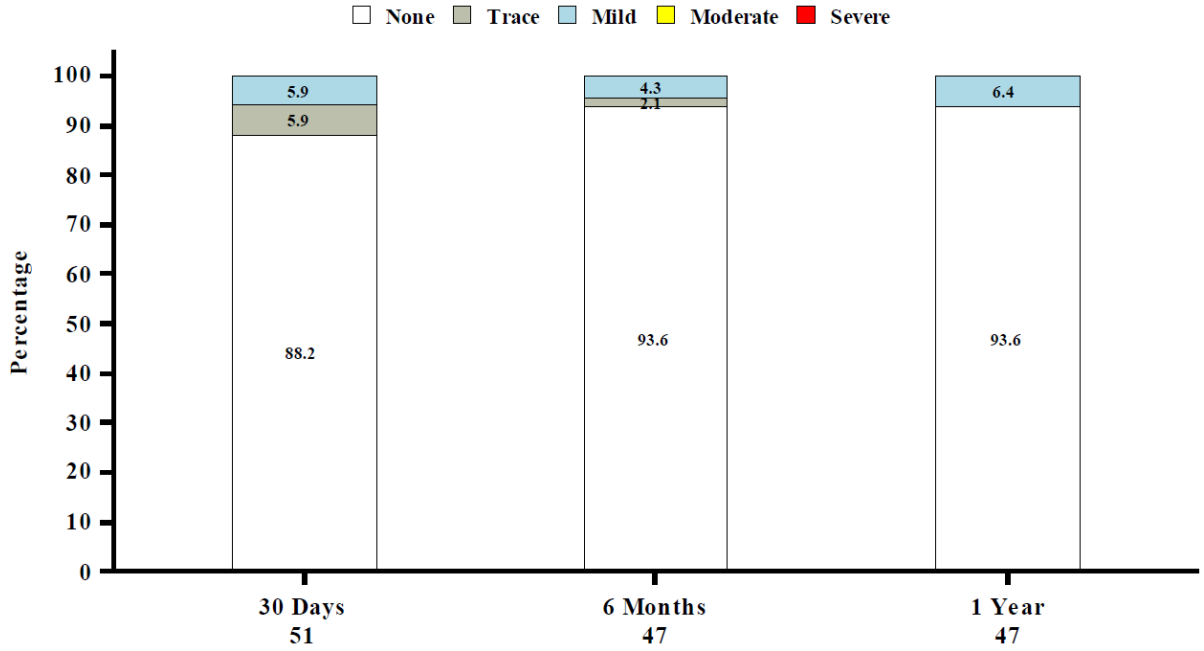
Note: Line plot with mean and standard error. The total number of subjects at each visit time point only counted the subjects with valid values.

Figure 8: Total Pulmonary Regurgitation (VI Population)



Note: The total number of subjects at each visit time point only counted the subjects with valid values.

Figure 9: Paravalvular Regurgitation (VI Population)

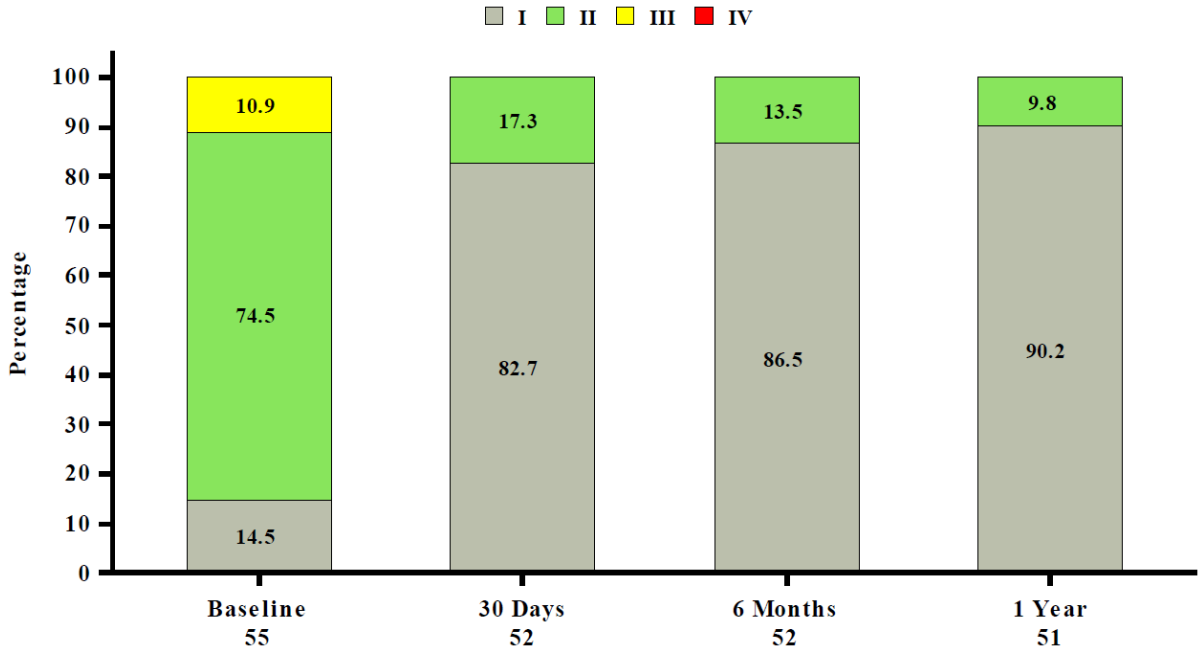


Note: The total number of subjects at each visit time point only counted the subjects with valid values.

NYHA Functional Class

The NYHA classifications by visit are presented in Figure 10. At baseline, 89.1% of subjects were in NYHA Class I/II. At 1 year, all subjects were in NYHA Class I/II.

Figure 10: NYHA Class by Visit (VI Population)



4. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 12.

Table 12: CEC-Adjudicated Adverse Events Through 1 Year (AT Population)

Event	Summary Statistics*		
	30 Days (N=57)	6 Months (N=55)	1 Year (N=51)
Death	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cardiovascular	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Non-Cardiovascular	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Reintervention†	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Arrhythmia	3.4% (2,2)	7.1% (5,4)	7.1% (5,4)
Permanent Pacemaker	0.0% (0,0)	1.8% (1,1)	1.8% (1,1)
Acute Kidney Injury	0.0% (0,0)	--	--
Bleeding	10.3% (6,6)	--	--
Life Threatening or Disabling	0.0% (0,0)	--	--
Major	0.0% (0,0)	--	--
Minor	10.3% (6,6)	--	--
Coronary Artery Compression	0.0% (0,0)	--	--

Event	Summary Statistics*		
	30 Days (N=57)	6 Months (N=55)	1 Year (N=51)
Endocarditis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Myocardial Infarction	0.0% (0,0)	--	--
Pulmonary Embolism	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Stroke	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
TIA	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Vascular Injury or Access Site Complication	12.1% (7,7)	--	--
Major	0.0% (0,0)	--	--
Minor	12.1% (7,7)	--	--

*Kaplan-Meier estimate (No. events, No. patients with event)
†Includes reintervention for both RVOT conduit and THV

5. Other Study Observations

Procedural Information

Procedural data are summarized in Table 13. General anesthesia was used in the majority of subjects (91.4%). Pre-stenting occurred in 53.4% of the procedures. The most frequent procedural complication was RVOT conduit tear, which occurred in 8.6% of patients. The interventions associated with these procedural complications are summarized in Table 14.

Table 13: Procedural Data (AT Population)

Variable	Summary Statistics* (N=58)
Catheterization laboratory time (min)	238.2 ± 92.5 (58)
Procedure time (min)	120.4 ± 97.8 (57)
Anesthesia time (min)	227.7 ± 93.3 (55)
Type of anesthesia used	
General	91.4% (53/58)
Conscious sedation	8.6% (5/58)
Planned concomitant procedures	6.9% (4/58)
Procedural complications	12.1% (7/58)
RVOT conduit tear	8.6% (5/58)
Difficulty removing delivery system	1.7% (1/58)
Difficulty advancing the delivery system	1.7% (1/58)
Pre-dilatation performed	79.3% (46/58)
Pre-stenting performed	53.4% (31/58)
Any stent placed	53.4% (31/58)
Stent placed during procedure	53.4% (31/58)
SAPIEN 3 THV implanted	96.6% (56/58)

Variable	Summary Statistics* (N=58)
20 mm	19.6% (11/56)
23 mm	37.5% (21/56)
26 mm	37.5% (21/56)
29 mm	5.4% (3/56)
Post-dilatation performed	26.8% (15/56)
Valve not fully expanded	86.7% (13/15)
Other	13.3% (2/15)
Second SAPIEN 3 THV implanted	1.8% (1/57)

*Continuous measures - Mean ± SD (Total no.); categorical measures - % (no./Total no.)

Table 14: Procedural Complication Interventions

Variable	Summary Statistics* (N=58)
Action taken to resolve complication	
Transcatheter implant of commercial valve	1.7% (1/58)
Placement of covered stent	6.9% (4/58)
Other	3.4% (2/58)
Venotomy to remove ruptured balloon	1.7% (1/58)
Prolonged intubation	1.7% (1/58)

*Categorical measures - % (no./Total no.)

Subgroup Analyses

The pre-specified subgroup analyses by age, gender, valve size, and pre-stenting are summarized in Table 15.

Table 15: THV Dysfunction at 1 Year: Subgroup Analysis (VI Population)

Subgroup	Endpoint	Summary Statistics* (N=56)
By Age Group		
≤ 21 (N=12)	THV Dysfunction	0.0% (0/11)
	RVOT reintervention	0.0% (0/12)
	Moderate or greater PR	0.0% (0/11)
	Mean RVOT gradient >40 mmHg	0.0% (0/11)
≥ 22 (N=44)	THV Dysfunction	5.6% (2/36)
	RVOT reintervention	0.0% (0/44)
	Moderate or greater PR	2.8% (1/36)

Subgroup	Endpoint	Summary Statistics* (N=56)
	Mean RVOT gradient >40 mmHg	2.7% (1/37)
By Gender		
Female (N=18)	THV Dysfunction	0.0% (0/17)
	RVOT reintervention	0.0% (0/18)
	Moderate or greater PR	0.0% (0/17)
	Mean RVOT gradient >40 mmHg	0.0% (0/17)
Male (N=38)	THV Dysfunction	6.7% (2/30)
	RVOT reintervention	0.0% (0/38)
	Moderate or greater PR	3.3% (1/30)
	Mean RVOT gradient >40 mmHg	3.2% (1/31)
By Valve Size		
20mm (N=11)	THV Dysfunction	22.2% (2/9)
	RVOT reintervention	0.0% (0/11)
	Moderate or greater PR	11.1% (1/9)
	Mean RVOT gradient >40 mmHg	11.1% (1/9)
23mm (N=21)	THV Dysfunction	0.0% (0/17)
	RVOT reintervention	0.0% (0/21)
	Moderate or greater PR	0.0% (0/17)
	Mean RVOT gradient >40 mmHg	0.0% (0/17)
26mm (N=21)	THV Dysfunction	0.0% (0/18)
	RVOT reintervention	0.0% (0/21)
	Moderate or greater PR	0.0% (0/18)
	Mean RVOT gradient >40 mmHg	0.0% (0/19)
29mm (N=3)	THV Dysfunction	0.0% (0/3)
	RVOT reintervention	0.0% (0/3)
	Moderate or greater PR	0.0% (0/3)
	Mean RVOT gradient >40 mmHg	0.0% (0/3)
By Pre-stenting		
Pre-stented (N=31)	THV Dysfunction	8.0% (2/25)
	RVOT reintervention	0.0% (0/31)
	Moderate or greater PR	4.0% (1/25)
	Mean RVOT gradient >40 mmHg	4.0% (1/25)
No pre-stent (N=25)	THV Dysfunction *	0.0% (0/22)
	RVOT reintervention	0.0% (0/25)
	Moderate or greater PR	0.0% (0/22)
	Mean RVOT gradient >40 mmHg	0.0% (0/23)

*Categorical measures - % (no./Total no.)

6. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conduction clinical studies covered by the regulation. The COMPASSION S3 study involved 45 investigators of which none were full-time or part-time employees of the sponsor and 15 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f), as described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None
- Significant payment of other sorts: 15
- Proprietary interest in the product tested held by the investigator: None
- Significant equity interest held by investigator in sponsor of covered study: None

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM THE PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Transcatheter pulmonary valve replacement (TPVR) with the SAPIEN 3 THV System provides a less invasive alternative to surgical replacement of a dysfunctional RVOT conduit or surgical bioprosthetic valve in the pulmonic position to relieve PR and/or pulmonary stenosis. The results of the COMPASSION S3 study demonstrated the effectiveness of the SAPIEN 3 THV for this intended use. In the clinical study, the Kaplan-Meier estimate of the primary endpoint of THV dysfunction at 1 year was 4.3%, with an upper 95% confidence interval of 14.5%, which was lower than the prespecified performance goal of 25%; thus, the

primary endpoint was met. Hemodynamic improvement was demonstrated by the reduction in mean RVOT gradient and the reduction in severity of residual pulmonary regurgitation. Specifically, the mean RVOT gradient reduced on average from 28.0 mmHg at baseline to 14.2 mmHg at 1 year, and all but one subject (97.9%) had ≤ mild total PR at 1 year compared to 21.8% at baseline. Freedom from RVOT reintervention was 100% at 1 year. All subjects were NYHA functional class I/II (I: 90.2%; II: 9.8%) at 1 year compared to 89.1% (I: 14.5%; II: 74.5%) of subjects at baseline.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The results from the nonclinical laboratory (e.g., biocompatibility, hydrodynamic performance, durability, and structural integrity) and animal studies demonstrated that the SAPIEN 3 THV is suitable for long-term implant.

The results of the COMPASSION S3 study demonstrated overall low adverse event rates. Procedural complications occurred in 12.1% of the patients, including 5 (8.6%) RVOT conduit tears. Other adverse events included arrhythmia (3.4% at 30 days and 7.1% at 1 year), minor bleeding (10.3% at 30 days), and minor vascular injury or access site complication (12.1% at 30 days). Freedom from death was 100% at 1 year, as were freedoms from endocarditis, device migration or embolization, and valve explant. There were no events of coronary artery compression requiring intervention at 30 days. Additionally, there were no valve frame fractures at 1 year.

C. Benefit-Risk Determination

The probable benefits of TPVR with the SAPIEN 3 THV demonstrated in the COMPASSION S3 study include improved pulmonary valve hemodynamics and improvement in functional status as measured by the NYHA classification at one-year post-procedure. These improvements may delay the need for surgical replacement of the patient's dysfunctional RVOT conduit or surgical bioprosthesis in the pulmonic position. For patients that require multiple reoperations over a lifetime, with incremental increases in risk of surgical morbidity and mortality with each reoperation, TPVR with SAPIEN 3 THV may reduce the cumulative risks associated with such operations.

The probable risks of TPVR with the SAPIEN 3 THV include procedural complications and long-term risks such as major vascular complications, bleeding, endocarditis, and THV dysfunction.

1. Patient Perspectives

   This application did not include specific information on patient perspectives for TPVR with the SAPIEN 3 THV.

The clinical data support that for use in pediatric and adult patients with a dysfunctional RVOT conduit or surgical bioprosthetic valve in the pulmonic position, the probable benefits of TPVR with the SAPIEN 3 THV outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the SAPIEN 3 THV System with Edwards Commander Delivery System for the use in pediatric and adult patients with a dysfunctional RVOT conduit or surgical bioprosthetic valve in the pulmonic position.

XIII. CDRH DECISION

CDRH issued an approval order on August 31, 2020. The final conditions of approval cited in the approval order are described below.

The applicant must conduct two post-approval studies:

1. *SAPIEN 3 Pulmonic Long-term Follow-up Study*: This study will be conducted as per the protocol dated August 6, 2020, entitled "Edwards SAPIEN 3 Transcatheter Heart Valve System Pulmonic Indication Post-Approval Data Analysis Protocol: Continued Follow-up of IDE Cohorts." The study will consist of all subjects enrolled under IDE G150220, including the Continued Access Protocol subjects. The objective of the study is to characterize the clinical outcomes of these subjects annually through 5 years post-procedure. The safety and effectiveness endpoints include mortality, transcatheter heart valve (THV) dysfunction, THV hemodynamic function, THV frame fracture, and device-related endocarditis.

2. *SAPIEN 3 Pulmonic New Enrollment Study:* This study will be conducted as per the protocol dated August 7, 2020, entitled "Congenital Multicenter Trial of Pulmonic Valve Dysfunction Studying the SAPIEN 3 Interventional THV Post-Approval Study." The study will enroll a total of 150 subjects at up to 20 sites in the U.S. The objective of the study is to monitor the device performance and clinical outcomes of the SAPIEN 3 THV System with Edwards Commander Delivery System in the real world for the approved indication. Subjects will be followed for 5 years. The safety and effectiveness endpoints include device success, THV dysfunction, THV hemodynamic function, and New York Heart Association (NYHA) classification.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See final approved labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the final labeling (Instructions for Use).

Post-approval Requirements and Restrictions: See Approval Order.