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Engineering the extraordinary

Expectations and Challenges of HBD for Children

Reaching Pediatric Patients

Harmony Transcatheter Pulmonary Valve

Declan Dineen, VP Regulatory Affairs Medtronic Structural Heart

1 IN 100 BIRTHS RESULT IN A CONGENITAL HEART DEFECT

22% RVOT DYSFUNCTION

23 % RVOT CONDUIT (MELODY)

77% NATIVE PATCH REPAIR (HARMONY)

Harmony™ Transcatheter Pulmonary Valve Replacement

Product Overview

Transcatheter Pulmonary Valve (TPV)

- Porcine pericardial tissue valve
- Self-expanding nitinol frame
- Polyester cloth covering
- Differing valve sizes, inflow diameter, outflow diameter, and length to fit a range of patient anatomies

Delivery Catheter System (DCS)

- Coil loading system
- Loading funnel to collapse valve prior to sheathing
- Retractable sheath
- Manipulation of handles to facilitate unsheathing and release of TPV for final deployment

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Circulation Journal
doi:10.1253/circj.CJ-19-1092

ORIGINAL ARTICLE
Pediatric Cardiology and Adult Congenital Heart Disease

Partnership Between Japan and the United States for Early Development of Pediatric Medical Devices

— Harmonization By Doing for Children —

Sara Takahashi; Nicole Ibrahim, PhD; Satoshi Yasukochi, MD; Richard Ringel, MD; Frank Ing, MD; Hideshi Tomita, MD; Hisashi Sugiyama, MD; Masaaki Yamagishi, MD; Thomas J. Forbes, MD; Sung-Hae Kim, MD; Mami Ho, MD; Nicole Gillette; Yasuko Nakamura; Koji Mineta; Neal Fearnot, PhD; Declan Dineen; Eric Vang, PhD; Russel Haskin; Lisa A. M. Becker, PhD; Kazuaki Sekiguchi, PhD; Kisaburo Sakamoto, MD; Carlos E. Ruiz, MD, PhD
on behalf of the Harmonization by Doing for Children Working Group

Background: The Harmonization By Doing (HBD) program was established in 2003 as a partnership among stakeholders of academia, industry and regulatory agencies in Japan and the United States, with a primary focus on streamlining processes of global medical device development for cardiovascular medical devices. While HBD has traditionally focused on development of devices intended to treat conditions prevalent in adults, in 2016, HBD established the "HBD-for-Children" program, which focuses on the development of pediatric devices as the development of medical devices for pediatric use lags behind that of medical devices for adults in both countries.

Methods and Results: Activities of the program have included: (1) conducting a survey with industry to better understand the challenges that constrain the development of pediatric medical devices; (2) categorizing pediatric medical devices into five categories based on global availability and exploring concrete solutions for the early application and regulatory approval in both geographies; and (3) facilitating global clinical trials of pediatric medical devices in both countries.

May 1, 2019

Medtronic, Inc.
Ms. Meghan Call
Regulatory Affairs Specialist
3576 Unocal Place
Santa Rosa, California 95403

Re: Q190583
Trade/Device Name: Harmony Transcatheter Pulmonary Valve System
Received: April 1, 2019

Dear Ms. Call:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received the above submission requesting designation as a Breakthrough Device. The proposed indications for use includes "the treatment of symptomatic severe pulmonary regurgitation in patients with a surgically-repaired right ventricular outflow tract." We are pleased to inform you that your device and proposed indication for use meet the criteria and have been granted designation as a Breakthrough Device. Please refer to the FDA guidance document entitled "Breakthrough Devices Program", for more information regarding the program, available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf.

FDA NEWS RELEASE

FDA Approves First in the World Device to Treat Patients with Congenital Heart Disease

New implant device provides less invasive option to treat pulmonary valve regurgitation for patients with a native or surgically-repaired right ventricular outflow tract

For Immediate Release: March 26, 2021

Español

Today, the U.S. Food and Drug Administration approved the first in the world non-surgical heart valve to treat pediatric and adult patients with a native or surgically-repaired right ventricular outflow tract (RVOT), the part of the heart that carries blood out of the right ventricle to the lungs. The device is designed for patients who have severe pulmonary valve regurgitation (blood leaking backward into the right lower chamber of the heart), a condition that often results from congenital heart disease. The device, called the Harmony Transcatheter Pulmonary Valve (TPV) System, is intended to improve blood flow to the lungs in patients with severe pulmonary valve regurgitation without open-heart surgery, which is the current standard of care. The use of the Harmony valve may delay the

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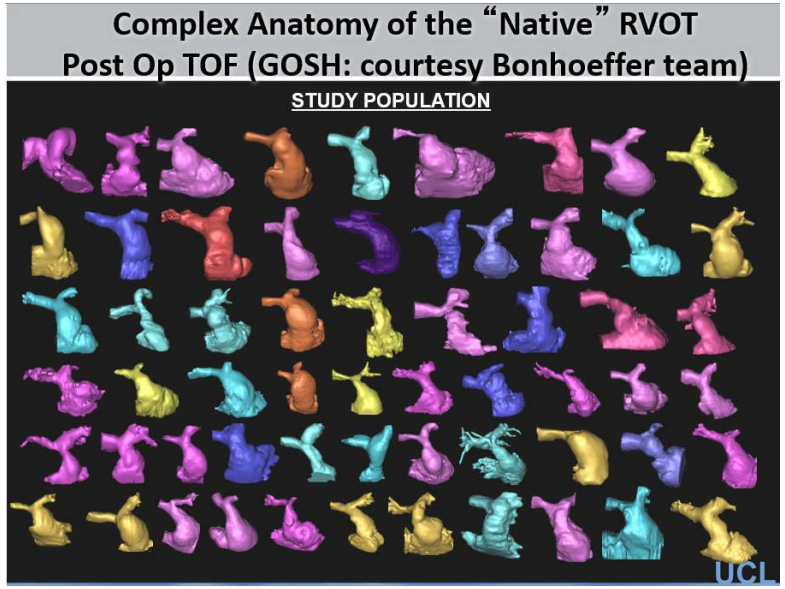
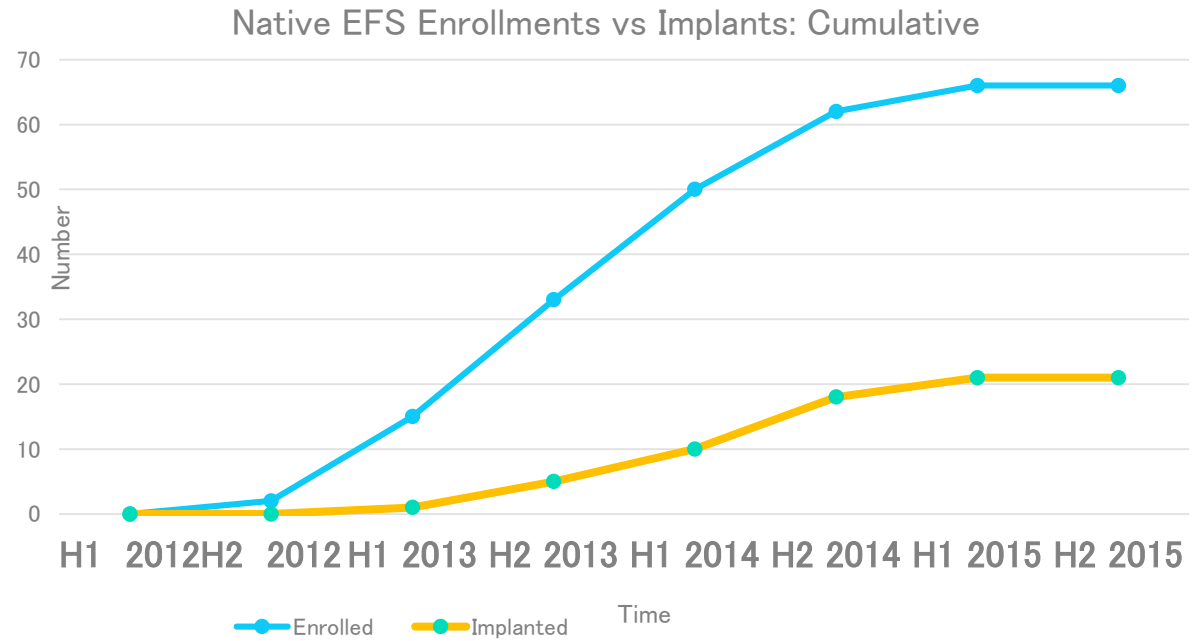
Original Landscape

- MDT wished to build on our Melody experience to offer a TPV product that served non-conduit patients in native anatomy
- Mission driven program addressing an underserved patient population
- Challenges
  - Small, heterogenous patient population
  - Versatile design to fit a wide variety of patient RVOT anatomies
  - Enrollment extremely challenging
  - Limited alignment among global regulators
- Viability of program in question





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HBD For Children

HBD for Children Program

- HBD established in 2003 as a partnership among stakeholders of academia, industry and regulatory agencies in Japan and the United States,
- HBD for Children established in 2016 with a primary focus on the development of pediatric devices as the development of medical devices for pediatric use lags behind that of medical devices for adults in both countries

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HBD for Children
HARMONY PROOF OF CONCEPT GOALS

Classification of Pediatric Medical Devices With High Medical Needs Category	
Category	**Details**
1	Approved in the United States but not approved in Japan
2	Not approved but used as off-label in the United States and Japan for a long time
3	Not approved and not used in the United States and Japan but used/approved in other countries
4	Under development
5	Approved in Japan but not approved in the United States

Harmony selected as Proof of Concept (PoC) for Category 4

- Medical devices currently under development and not approved anywhere in the world

Goals Include:

- Conduct of global clinical trials enrolling patients worldwide using harmonized study protocols
- Facilitate more expeditious development and marketing of pediatric devices in both countries

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HBD Experience
PERFORMANCE TO HBD GOALS

Conduct of global clinical trials enrolling patients worldwide using harmonized study protocols

- Singular pivotal study protocol

Facilitate more expeditious development and marketing of pediatric devices in both countries

- Parallel commercial review

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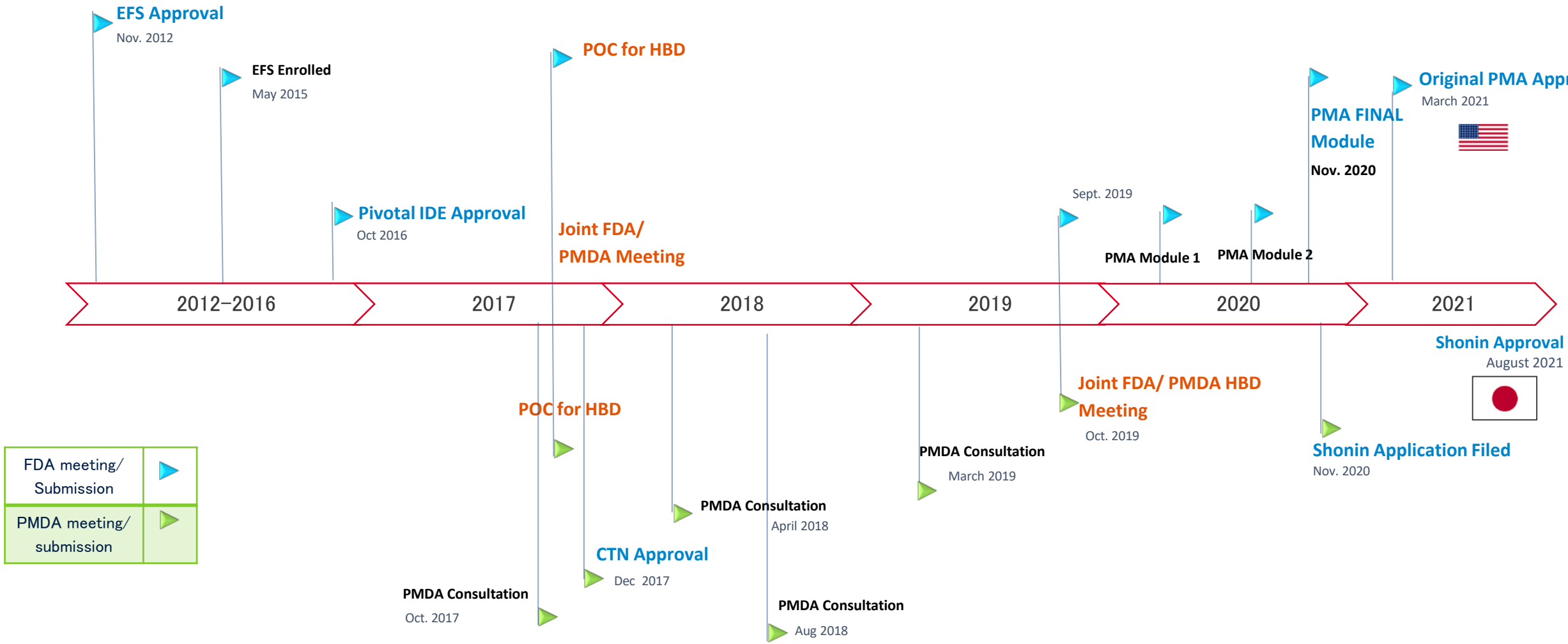
History of Interactions



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HBD Experience
WHAT WORKED WELL

- Practical solutions to several challenges typical of pediatric programs
  - Achievable pivotal study design & sample size determined based on target patient population
  - Post market study
  - Ability to iterate during study
  - Accelerating innovation

- Agency prioritization and cooperation
  - Breakthrough Design Designation (US)
  - Orphan product (Japan)
  - Interactive review – facilitate innovation & accelerated review
  - Joint agency interaction

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Challenges

- Significant investment of time and resources
  - Group level discussions
  - Individual regulatory/ company/ academia discussions
  - Joint discussions
- Parallel Original PMA & Shonin applications is a significant undertaking
- HBD focuses on the regulatory process and does not consider differences in medical practice

Recommendations

- Discuss any differences in medical practice proactively and jointly with both agencies
  - *A priori* agreement of:
    - patient population
    - Indication
    - Patient selection criteria
    - Preoperative assessment methods
- Reduction in burden continues to be important e.g., interactive review, pre-approval inspection, post approval commitments
- PMDA & FDA collaboration on GCP inspection
- Expand HBD to include other regions

Conclusions

- Practical mechanism to expand the market by pursuing effective harmonized multiregional regulatory & clinical strategy
- Global regulatory agency cooperation with academia and industry can reduce development time and time to market for pediatric products
- Program would not have succeeded without academia, FDA & PMDA support

Thank you

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