Presentation to the Pediatric Advisory Committee
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Contegra® Pulmonary Valved Conduit

Humanitarian Device Exemption (HDE) H020003

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Device Description

- A glutaraldehyde-crosslinked, heterologous bovine jugular vein with a competent tri-leaflet venous valve.

- Indications for Use
  - Correction or reconstruction of the right ventricular outflow tract in patients aged < 18 years with any of the following congenital heart malformations:
    - Pulmonary Stenosis (PS)
    - Tetralogy of Fallot (TOF)
    - Truncus Arteriosus (TA)
    - Pulmonary Atresia (PA)
    - Transposition with Ventricular Septal Defect (VSD)
  - Replacement of previously implanted, but dysfunctional, pulmonary homografts or valved conduits

Medical Device Report (MDR) Review

MDR: Primary Reported Problem

by Patient Age and TTEO*

Primary Reported Problem 06/01/15 – 05/31/16	Total MDR Count	Patient Age (years)			TTEO (months)	
		Pediatric (<22)	Adult (≥ 22)	Age not reported	Range	Mean
Stenosis	28	26	1	1	0.2-165	76
Device replacement** (reason not provided)	22	17	3	2	2.7-120	74
Regurgitation	2	1	0	1	0-112	56
Infection/Endocarditis	2	1	1	0	2-102	52
Conduit tear/breakdown	2	1	0	1	0-33	17
Increased pressure gradients	1	1	0	0	101	--
Device sizing issue	1	1	0	0	0.2	--
Total	**58**	**48**	**5**	**5**		

* TTEO: Time to Event Occurrence

** ”Replacement “ refers to the interventions taken to replace or substitute the function of Contegra device, e.g. replacing the Contegra surgically or via a transcatheter valve-in-valve procedure, without removing the Contegra device.

MDR: Primary Reported Problem

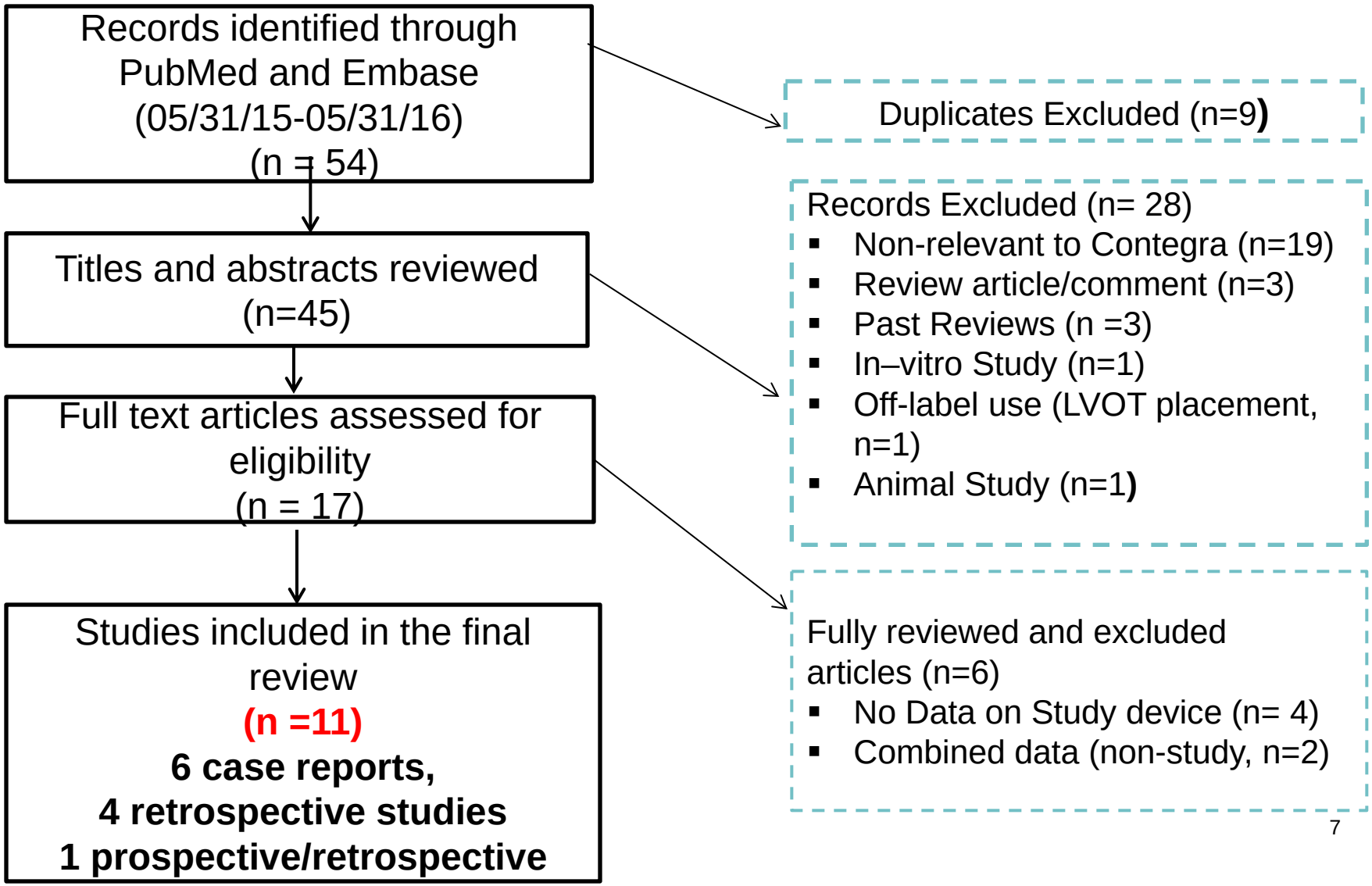
Comparison of MDRs in 2015 and 2016

Primary Reported Problem	2015 PAC MDR Count (%)	2016 PAC MDR Count (%)
Stenosis	12 (40%)	28 (48%)
Device replacement (reason not provided)	5 (17%)	22 (38%)
Regurgitation*	2 (6.7%)	2 (3.4%)
Infection/Endocarditis	1 (3.3%)	2 (3.4%)
Conduit tear/breakdown	1 (3.3%)	2 (3.4%)
Increased pressure gradients	2 (6.7%)	1 (1.7%)
Device sizing issue	4 (13.4%)	1 (1.7%)
Thrombus	1 (3.3%)	0
Bleeding	1 (3.3%)	0
Death	1 (3.3%)	0
Total	**30**	**58**

* Regurgitation category includes the reports noting valve regurgitation, insufficiency, or incompetence.

Literature Review

Article Selection



Pediatric-Only Studies

Sarikouch et al, 2016

		Rate at 5-years	Rate at 10 years
Freedom from Death	Contegra (n=93)	95.9%	95.9%
	DPH (n=93)		
	CH (n=93)		
Freedom from Explantation	Contegra (n=93)	***90.1%***	***84.3%***
	DPH (n=93)	***100%***	***100%***
	CH (n=93)	90.0%	84.2%
Freedom from Explantation and Gradient ≥ 50mmHg	Contegra (n=93)	***60.4%***	***48.5%***
	DPH (n=93)	***85.9%***	***85.9%***
	CH (n=93)	***79.9%***	***63.5%***
Freedom from Moderate Insufficiency	Contegra (n=93)	77%	52%
	DPH (n=93)	81%	-
	CH (n=93)	75%	51%
Freedom from Endocarditis	Contegra (n=93)	94.4%	*94.4%*
	DPH (n=93)	100%	100%
	CH (n=93)	97.1%	97.1%

- DPH = decellularized pulmonary homograft; CH = cryopreserved homograft
- ***Bold/ itallicized*** numbers represent statistically significant differences between Contegra outcomes and DPH outcomes

Kido et al, 2016

	Rate Through 10 Months Follow-up (n=13)
Mortality	15.4%
Freedom from Reoperation	53.8%

Mixed Pediatric/Adult Studies

Mery et al (2016) – Reintervention and Replacement

	Re-intervention		Replacement	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Pulmonary Homograft (n=289)	Reference		Reference	
Aortic Homograft (n=121)	1 (0.88-1.14)	0.9588	0.91(0.63-1.33)	0.6251
Contegra (n=245)	0.54 (0.4-0.73)	<0.0001	0.51 (0.36-0.73)	0.0002
Porcine Heterograft (n=137)	0.9 (0.59-1.39)	0.6414	0.94 (0.59-1.49)	0.7805

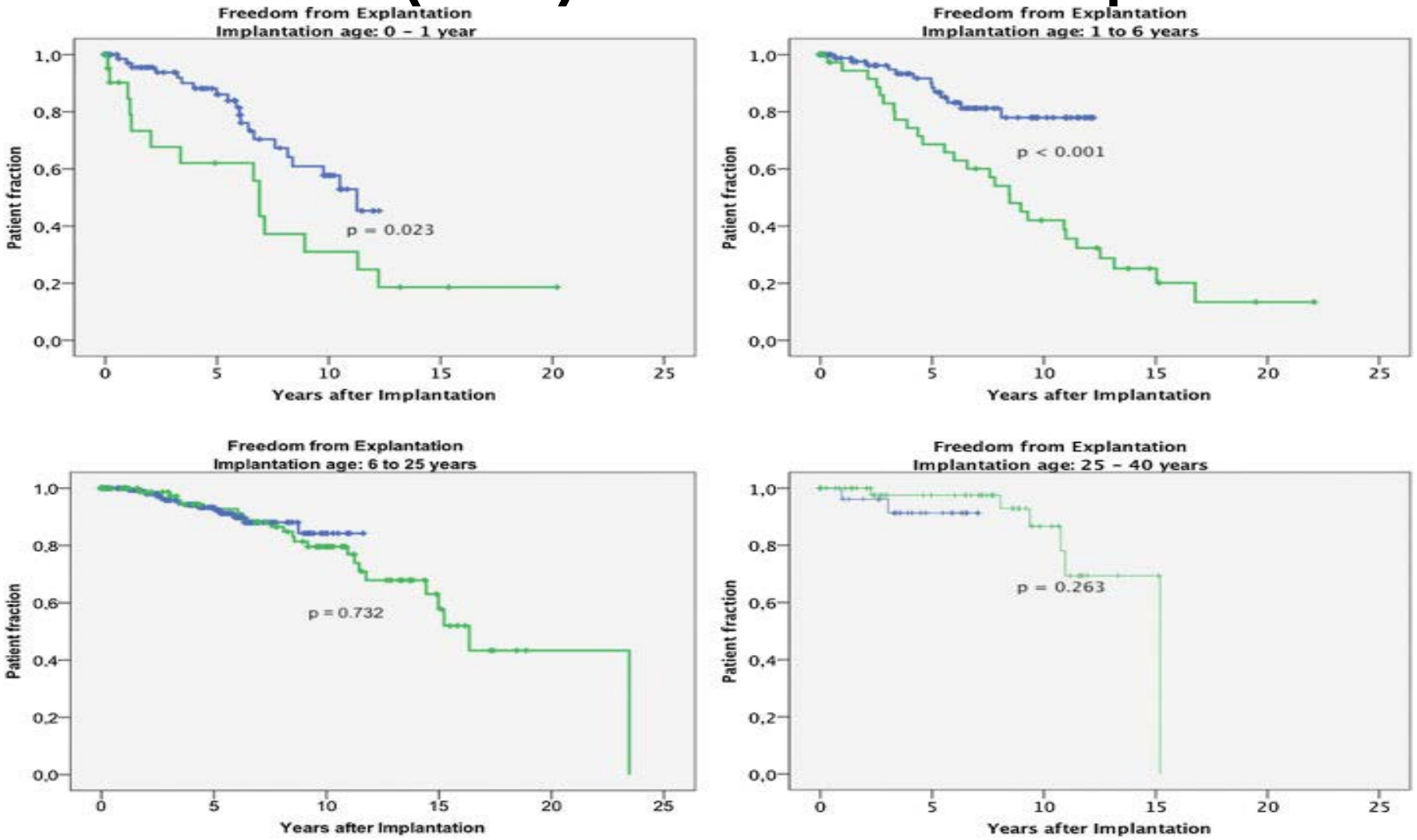
Median follow-up 7 years;
HR = hazard ratio

Mery et al (2016) – Freedom from Endocarditis

Conduit type	Rate of Freedom from Endocarditis At 10 Years
Contegra (n=245)	83%
Pulmonary homograft (n=289)	98%
Aortic homograft (n=121)	100%
Porcine heterograft (n=137)	95%

*Risk of Endocarditis Contegra vs. Homografts: hazard ratio 9.05 (95% CI: 2.57-31.83, P = 0.0006)

Sandica et al (2016)- Freedom from Explantation



Conterga Homograft

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Additional Adverse Events Noted in Studies and Case Reports

- Coronary compression (Kido); n=1
  - Cardiogenic shock 6 months after implantation
  - Left main obstruction relieved by device explantation
- Thrombosis (Bilal); n=1
  - Right ventricle to Contegra conduit at 1 month
  - Thromboembolectomy
- Conduit dissection (Buelow); n=1
  - Acute heart failure 4 months after implantation
  - Conduit excised and replaced with PH
- Protrusion between sternal edges, external compression (Maddali); n=1
  - Secondary to size mismatch
  - Pectus carinatum deformity created to accommodate graft and reduced at 7 weeks

Literature Summary

- Limitations
  - Majority of studies were retrospective. Thus covariates were not balanced in comparing Contegra, Homograft, or in porcine heterograft in at least one study.
  - Follow-up times varied in comparing Contegra to other conduits, which could influence observed rates.
  - Contegra conduits were implanted over a long time frame (1999 - 2014) and the standard of care could have changed during this period of time.

Literature Summary

- Pediatric-Only Studies

  Compared to homograft, Contegra showed:

  - Lower rate of freedom from explantation and high pressure gradient ≥ 50 mmHg
  - Comparable rate of freedom from moderate insufficiency,
  - Comparable rate of freedom from endocarditis

- Pediatric/adult Studies

  Compared to homograft or other conduit, Contegra showed

  - Lower risk of re-intervention and replacement
  - Higher rate of freedom from explantation in patients younger than 1year and 1- 6 years old
  - Lower rate of freedom from endocarditis

CDRH Summary and Recommendations

- No new safety concerns identified.
  - Rates of endocarditis are consistent with data previously reported in the literature

- The HDE remains appropriate for the pediatric patient population for which it was granted.

- FDA will continue surveillance and report the following to the PAC in 2017:
  - Distribution numbers
  - MDR review results
  - Literature review results

Question to the PAC

- Does the Committee agree with CDRH's conclusions and recommendations?