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**Acorn Cardiovascular, Inc.**  
**CorCap™ Cardiac Support Device (P040049)**  
**Medical Devices Dispute Resolution Panel**  
**December 15, 2006**

# ACORN CARDIOVASCULAR AGENDA

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## **Opening Remarks**

Karen M. Becker, PhD

## **Summary of Clinical Data in PMA**

Mariell Jessup, MD

## **Expert Comment on Scientific Issues in Dispute**

### **Statistical and Trial Methodology**

Steven Piantadosi, MD, PhD

Donald B. Rubin, PhD

### **Cardiology**

Randall C. Starling, MD, MPH

Douglas L. Mann, MD

### **Cardiothoracic Surgery**

Steven F. Bolling, MD

Michael A. Acker, MD

## **Conclusions**

Steven Piantadosi, MD, PhD

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# **OPENING REMARKS**

Karen M. Becker, PhD  
Becker & Associates Consulting, Inc.  
**For: Acorn Cardiovascular, Inc.**

# OPENING REMARKS

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- MDDRP Process
- CorCap CSD Background Information
  - Device Description and Indications for Use
  - CorCap CSD Administrative Record
- New Information Available to MDDRP
- Clarifications for the Record
  - Missing Data
  - Blinding
- Standards for Review of PMAs
- Basis for Approvability of PMA

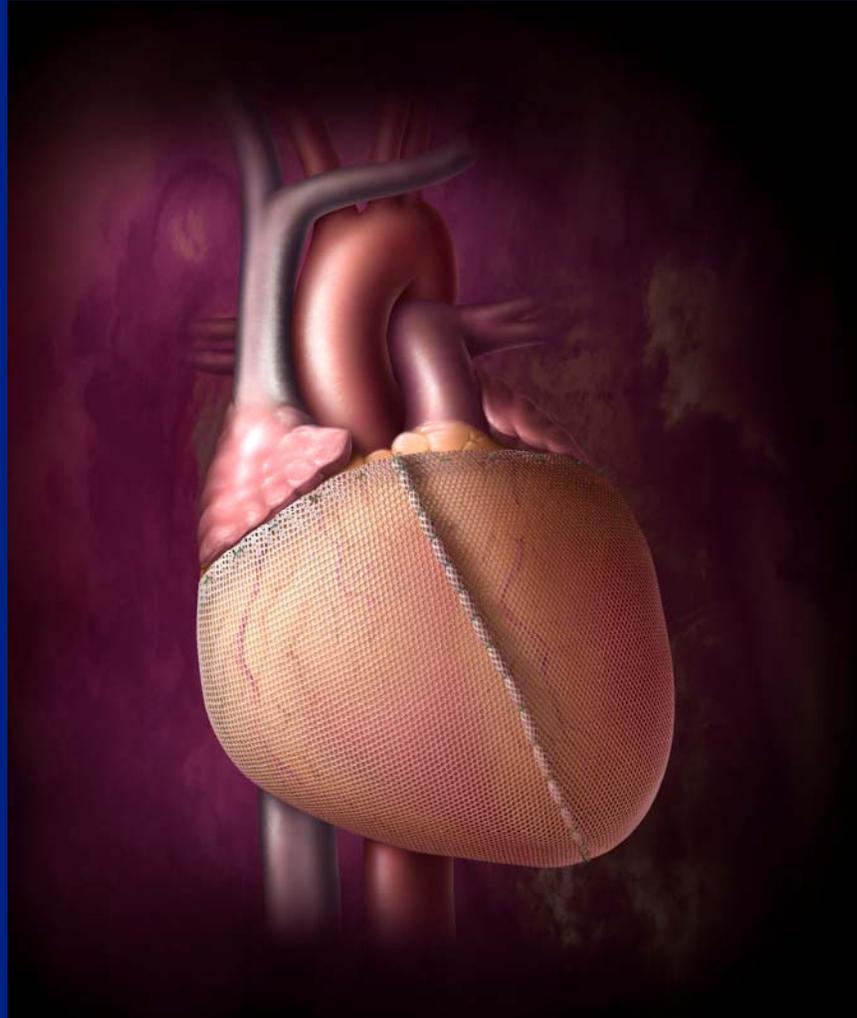
# MDDRP PROCESS

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- FDAMA 1997
- CDRH establishes Medical Devices Dispute Resolution Panel (MDDRP)
- Requires sound scientific grounds
- Matter sufficiently complex to warrant specialized experts and independent review
- Convened only once before

# CORCAP CARDIAC SUPPORT DEVICE

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# INDICATIONS FOR USE

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- Indications for use:
  - Indexed left ventricular end diastolic dimension  $\geq 30$  mm/m<sup>2</sup> and  $\leq 40$  mm/m<sup>2</sup>
  - LVEF  $\leq 35\%$  (or  $\leq 45\%$  if planned mitral valve repair or replacement)

# SCIENCE UNDERLYING CORCAP CSD TECHNOLOGY

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- Laboratory studies:
  - Myocardial cell structure and function, histology, biochemistry and molecular gene products
  
- Proof of concept studies in animal models of heart failure
  - Dog model: reduced LVEDV, increased LVEF, improved cardiomyocyte contraction and relaxation, down-regulation of stretch response proteins, increased affinity of the pump for calcium
  - Ovine model: maintenance or reduction in heart size, increased LVEF, fractional shortening and peak positive dP/dt
  - Sheep model of HF produced by ligation of coronary arteries (i.e., only mild dilation): consistent findings of reduced ventricular size and improved ventricular function

# REGULATORY HISTORY OF CORCAP PMA

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- December 2004: PMA submitted
- June 2005: CSD Panel votes 9 to 4 against approval
  - Missing data
  - Clinical relevance of primary endpoint
  - Safety
- August 2005: FDA issues not-approvable letter
- October 2005: Acorn submits Major Amendment to PMA
- February 2006: FDA issues not-approvable letter

# NEW INFORMATION IS AVAILABLE TO MDDRP

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- Amended PMA provides:
  - Data on potential investigator bias re: MCPs
  - Supplemental information on safety (re-operation)
  - Extended follow-up on mortality
  - Postmarketing study for safety and long-term outcomes
  - Post-hoc analysis of patients most likely to benefit
  - Revised indication for use based on ventricular size
- Imputation methodology: details and independent validation
- FDA agrees missing data is no longer a major concern
- Written testimony submitted by well-qualified experts

# CLARIFICATIONS OF ADMINISTRATIVE RECORD

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- Multiple imputation is statistically valid approach, and analysis is robust
- FDA required blinded NYHA assessment
- Study analysis plan was amended after study initiation at FDA request, but prepared prior to database lock and unblinding

# FDA REQUIRED CHANGE TO DATA ANALYSIS PLAN AT STUDY END

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- For ITT analysis of blinded NYHA, imputations relying on site (unblinded) NYHA were not acceptable to FDA

“For primary analyses, it is not acceptable to use two unblinded assessments or to use one blinded and one unblinded assessment.”

[Letter from Bram D. Zuckerman, M.D., Director, DCD, ODE to Janell Colley, Acorn Cardiovascular, May 19, 2004]

- Multiple imputation was recommended

# STANDARD TO BE APPLIED

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- Reasonable assurance of safety: [21 CFR 860.7(d)(1)]
  - Based on valid scientific evidence, probable benefits to health under conditions of intended use, when accompanied by adequate directions and warnings against unsafe use, outweigh probable risks
  - Absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use
  
- Reasonable assurance of effectiveness: [21 CFR 860.7 (e)(1)]
  - Based upon valid scientific evidence, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results

# BASIS FOR APPROVABILITY OF CORCAP CSD PMA

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- Well-controlled and executed pivotal study
- Reasonable evidence of safety:
  - Mortality and AEs similar between groups
  - Indications for use/IFU revised to minimize risk of peri-operative mortality
- Reasonable evidence of effectiveness:
  - Success criteria for primary endpoint met
  - Secondary endpoints supportive
  - Preclinical studies, and safety trial, provide additional evidence
- Statistical methods applied to the trial are sound
  - Validated by independent experts
- 500 patient post-approval study

# SCIENTIFIC ISSUES IN DISPUTE

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1. Primary endpoint result demonstrates clinically relevant benefits.
2. Statistical analysis of primary endpoint is reliable.
3. Secondary endpoint results support study hypothesis.
4. Safety profile is reasonable in consideration of benefit.
5. Original patient population adequately addresses safety and effectiveness questions.
6. Focused cohort analysis is post-hoc, and not necessary for approval.