


# Vulnerable Plaque and Device Development - FDA CDRH Perspective -

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# Role of FDA CDRH

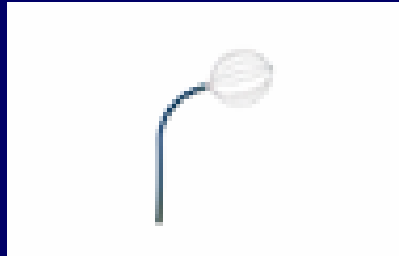
A black silhouette of the United States is centered on a light yellow rectangular background. The text is overlaid on this silhouette.

Establish reasonable  
assurance of the safety and  
effectiveness of medical devices  
marketed in the U.S.

# Risk-Based Paradigm

- Class I: common, low risk devices
  - general controls
  - most exempt from premarket submission
- Class II: more complex, higher risk
  - premarket notification [510(k)]
- Class III: most complex, highest risk
  - premarket approval application [PMA]

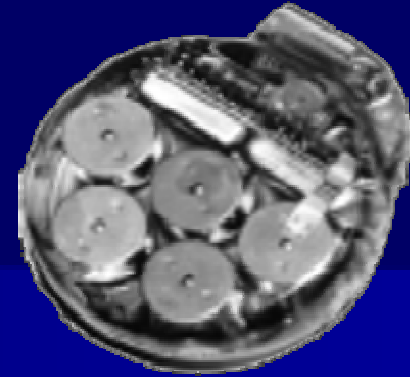
# 510(k)



- Lower risk devices
- Substantial equivalence
- 10-15% require clinical data
- Performance testing



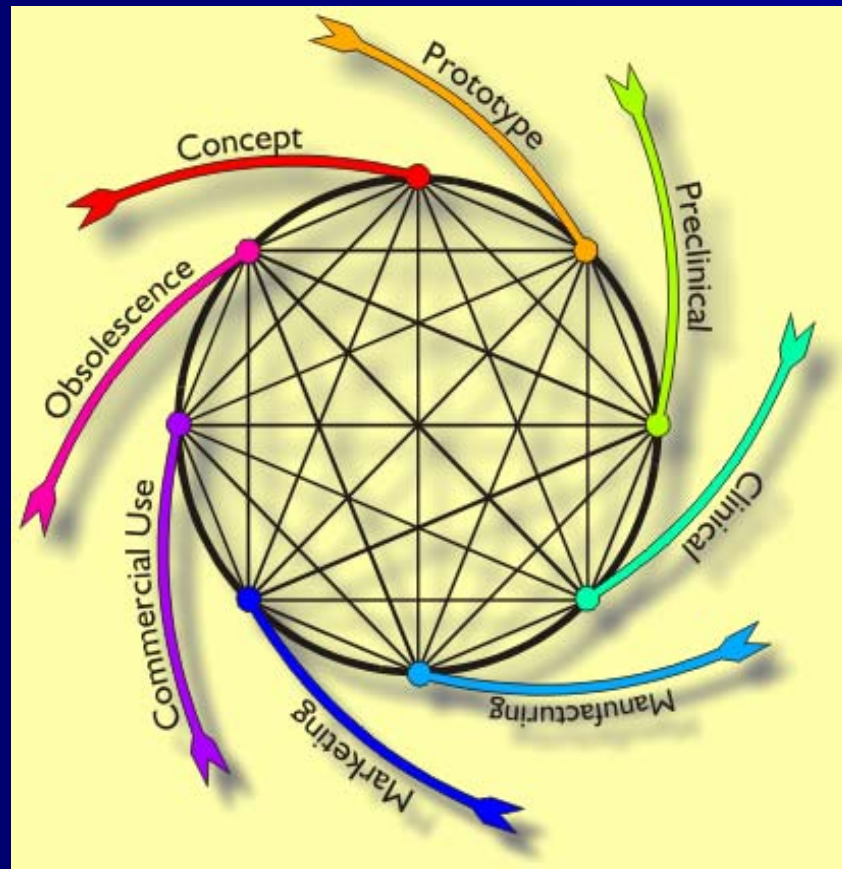
# PMA



- Higher risk devices
- Establish safety and effectiveness
- Bench - Animal - Human
- Similar to new drug approval process

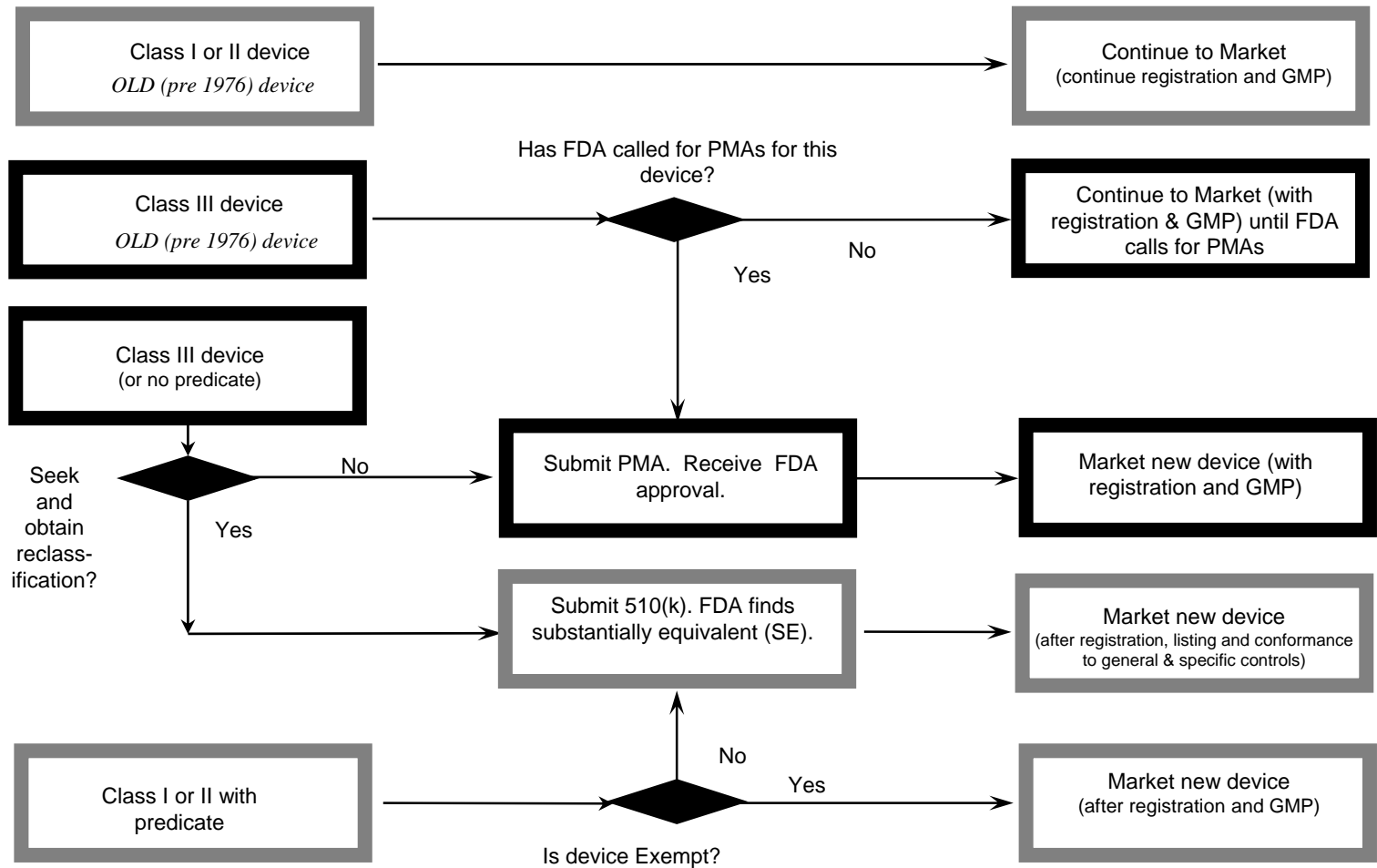


# CDRH Vision – Total Product Life Cycle



# What are the alternate routes to market?

Old device (marketed prior to May 1976) / New device (developed after May 1976)

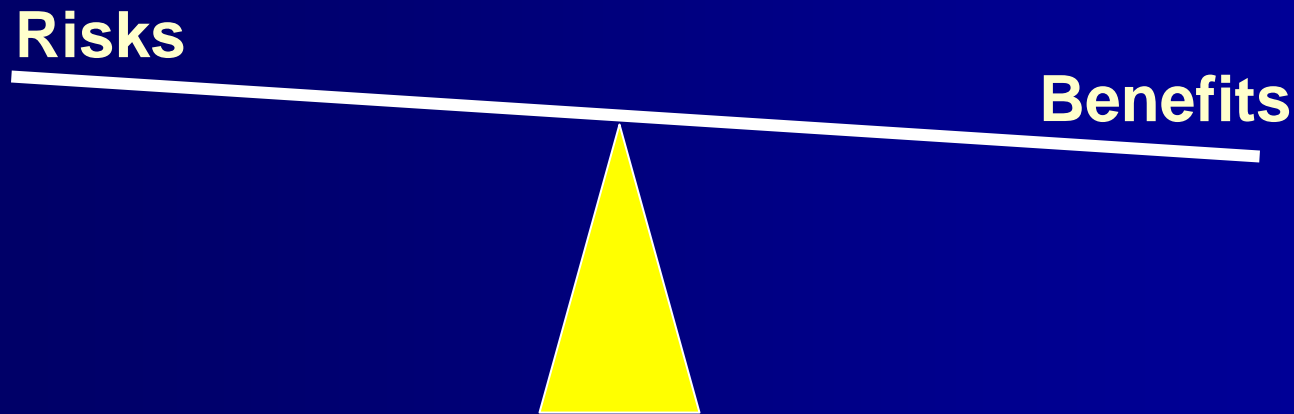


# Tool versus Clinical Claim

- “Tool” indications/claim
  - Device measures physiological parameter of interest
- “Clinical” (diagnostic) indications/claim
  - Parameter has predictive capability
  - Clinically-meaningful claim; obvious clinical utility
  - Generally need clinical validation to support claim
  - Usually more rigorous standard of evidence needed
- Consideration of Risk of Device Use

# Tool Claim

Inaccurate information causes  
small risk to patients...



...can be counterbalanced  
by small benefits

# Clinical/Diagnostic Claim

Misdiagnosis causes  
greater risk to patients...

**Risks**

**Benefits**



...needs to be counter-  
balanced by greater benefit

# Novel diagnostic catheters

- Tool/Functional indications
  - Display image of vessel wall / lumen
  - Evaluate local arterial compliance
  - Map temperature variation
- Diagnostic indications
  - Detect TCFA / vulnerable plaque
  - Predict risk / location of future ACS
  - Predict restenosis

# Novel diagnostic catheters test paradigm

- FDA Guidance document
  - “Guidance for Industry and FDA Staff – Coronary and Peripheral Arterial Diagnostic Catheters”, July 15, 2003
  - [www.fda.gov/cdrh/ode/guidance/1228.pdf](http://www.fda.gov/cdrh/ode/guidance/1228.pdf)
  - Reflects FDA’s current thinking on regulatory strategies

# General considerations

- Vulnerable plaque studies = currently limited by unproven detection methods and by lack of knowledge regarding natural history
  - Example - are lesions observed today the same lesions that cause future events?
- Consider collection of natural history data
  - Potential for addition to many study designs
  - Example: baseline and follow-up imaging data, plus imaging if / when there is a subsequent event

# General considerations – IDE's

- IDE is not required:
  - If a marketed device is used within its cleared/approved indication - e.g., data collected by IVUS
  - OR - if the study of an investigational device is Non-Significant Risk (NSR)
  - AND - if investigational, diagnostic data / analyses are not used to guide patient treatment
- FDA can issue a letter stating that a study is exempt / NSR and that an IDE is not required
- IRB approval may still be required if IDE not required

# Catheter safety evaluation

- Compare characteristics and use with existing devices.
- If significant differences -> risk analysis:
  - device design (radial force against art wall)
  - procedural method (plaque dislodgement during catheter withdrawal)
  - location of use (carotid versus femoral art)
  - anticipated arterial pathology (risk of plaque rupture and acute thrombosis)

# Catheter safety evaluation – clinical testing

- Staged test scheme:
  - initially test in relatively lower-risk patients
  - subsequently test in higher-risk population
- Example:
  - lower risk = femoral artery lesion or stable coronary insufficiency
  - higher risk - carotid artery lesions or acute coronary syndrome

# Potential Clinical Studies

1. Tool/Functional Claim - clinical safety and performance
2. Diagnostic Claim - predictive value / natural history
3. Diagnostic device - comparison to standard method
4. Diagnostic devices evaluated during "population" drug / device therapy
5. "Population" device therapy
6. Device therapy directed to a specific lesion

# 1. Tool / Functional Claim - clinical safety and performance

- Clinical safety / performance data = may be needed to support tool/functional claim
  - Example - “measures artery wall temperature”
  - Supports in-vitro / in-vivo safety & performance data
- Can results be compared to standard method?
- Where no standard – are results “as expected”?
  - e.g., do results differ as expected FOR: no visible lesions - vs. stable angina - vs. unstable angina / MI?
  - Are results concordant with other diagnostic tests?

# Thermal Heterogeneity Within Human Atherosclerotic Coronary Arteries Detected In Vivo

## A New Method of Detection by Application of a Special Thermography Catheter

Christodoulos Stefanadis, MD; Leonidas Diamantopoulos, MD; Charalambos Vlachopoulos, MD; Eleftherios Tsiamis, MD; John Dernellis, MD; Konstantinos Toutouzas, MD; Elli Stefanadi, MS; Pavlos Toutouzas, MD

**Background**—Activated macrophages play an important role in the pathogenesis of acute ischemic syndromes. It has been postulated that detection of heat released by activated inflammatory cells of atherosclerotic plaques may predict plaque rupture and thrombosis. Previous ex vivo studies have shown that there is thermal heterogeneity in human carotid atherosclerotic plaques.

**Methods and Results**—To measure the temperature of human arteries in vivo, we developed a catheter-based technique. Ninety patients (45 with normal coronary arteries, 15 with stable angina [SA], 15 with unstable angina [UA], and 15 with acute myocardial infarction [AMI]) were studied. The thermistor of the thermography catheter has a temperature accuracy of  $0.05^{\circ}\text{C}$ , a time constant of 300 ms, and a spatial resolution of 0.5 mm. Temperature was constant within the arteries of the control subjects, whereas most atherosclerotic plaques showed higher temperature compared with healthy vessel wall. Temperature differences between atherosclerotic plaque and healthy vessel wall increased progressively from SA to AMI patients (difference of plaque temperature from background temperature,  $0.106 \pm 0.110^{\circ}\text{C}$  in SA,  $0.683 \pm 0.347^{\circ}\text{C}$  in UA, and  $1.472 \pm 0.691^{\circ}\text{C}$  in AMI). Heterogeneity within the plaque was shown in 20%, 40%, and 67% of the patients with SA, UA, and AMI, respectively, whereas no heterogeneity was shown in the control subjects.

**Conclusions**—Thermal heterogeneity within human atherosclerotic coronary arteries was shown in vivo by use of a special thermography catheter. This heterogeneity is larger in UA and AMI, suggesting that it may be related to the pathogenesis. (*Circulation*. 1999;99:1965-1971.)

**Key Words:** ischemia ■ coronary disease ■ plaque ■ heat

# Incidence of High-Strain Patterns in Human Coronary Arteries

## Assessment With Three-Dimensional Intravascular Palpography and Correlation With Clinical Presentation

Johannes A. Schaar, MD; Evelyn Regar, MD, PhD; Frits Mastik; Eugene P. McFadden, MB, FRCPI; Francesco Saia, MD; Clemens Disco, MSc; Chris L. de Korte, PhD; Pim J. de Feyter, MD, PhD; Antonius F.W. van der Steen, PhD; Patrick W. Serruys, MD, PhD

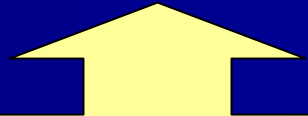
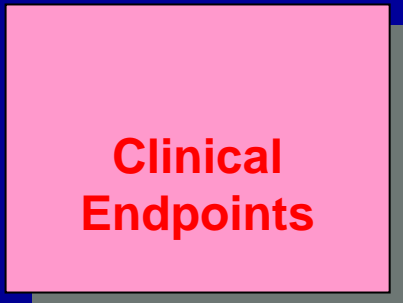
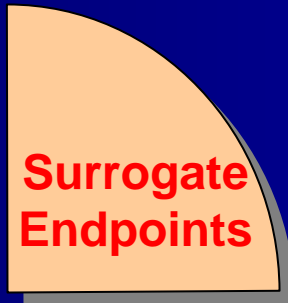
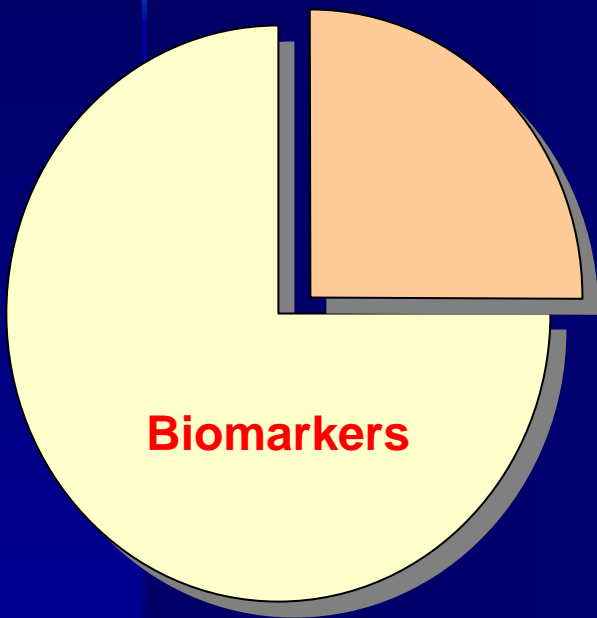
**Background**—Rupture of thin-cap fibroatheromatous plaques is a major cause of acute myocardial infarction (AMI). Such plaques can be identified in vitro by 3D intravascular palpography with high sensitivity and specificity. We used this technique in patients undergoing percutaneous intervention to assess the incidence of mechanically deformable regions. We further explored the relation of such regions to clinical presentation and to C-reactive protein levels.

**Method and Results**—Three-dimensional palpograms were derived from continuous intravascular ultrasound pullbacks. Patients (n=55) were classified by clinical presentation as having stable angina, unstable angina, or AMI. In every patient, 1 coronary artery was scanned (culprit vessel in stable and unstable angina, nonculprit vessel in AMI), and the number of deformable plaques assessed. Stable angina patients had significantly fewer deformable plaques per vessel ( $0.6 \pm 0.6$ ) than did unstable angina patients ( $P=0.0019$ ) ( $1.6 \pm 0.7$ ) or AMI patients ( $P<0.0001$ ) ( $2.0 \pm 0.7$ ). Levels of C-reactive protein were positively correlated with the number of mechanically deformable plaques ( $R^2=0.65$ ,  $P<0.0001$ ).

**Conclusions**—Three-dimensional intravascular palpography detects strain patterns in human coronary arteries that represent the level of deformation in plaques. The number of highly deformable plaques is correlated with both clinical presentation and levels of C-reactive protein. Further studies will assess the potential role of the technique to identify patients at risk of future clinical events (*Circulation*. 2004;109:2716-2719.)

**Key Words:** atherosclerosis ■ elasticity ■ plaque ■ ultrasonics ■ catheters

Evidence that a biomarker is reasonably likely to predict clinical benefit.



Evaluation of surrogate endpoint based on correlation with and capture of total treatment effect.

Modified from BDWG.

# Moving Forward

- Applicant (not FDA) decides: tool or clinical claim
- Early collaboration with FDA is key
- Pre-IDE submission:
  - contains clinical protocol, bench test scheme
  - FDA reviews and provides comments in writing, phone conference, face-to-face meeting
  - FDA advice, not requirement

# FDA Resources

- For general device questions:

[www.fda.gov/cdrh](http://www.fda.gov/cdrh)

- For specific advice:

Elias Mallis or Nick Jensen, DVM

[eym@cdrh.fda.gov](mailto:eym@cdrh.fda.gov)

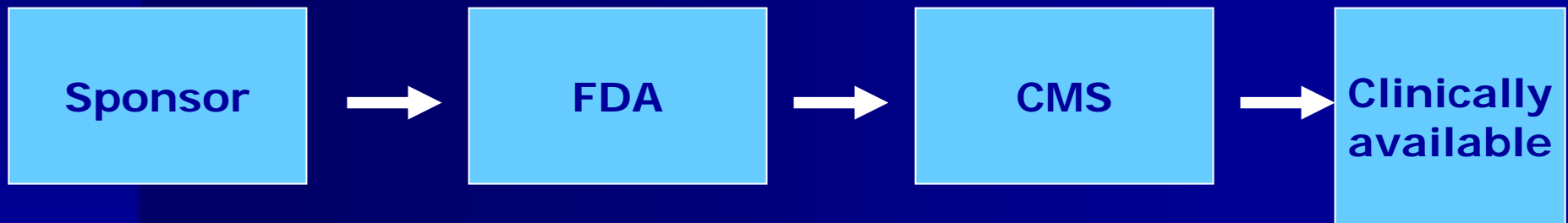
[dnj@cdrh.fda.gov](mailto:dnj@cdrh.fda.gov)

(301) 443-8517

# FDA and CMS Collaboration

# Old Paradigm

- CMS decision to provide Medicare coverage requires FDA approval
- *Sequential* process

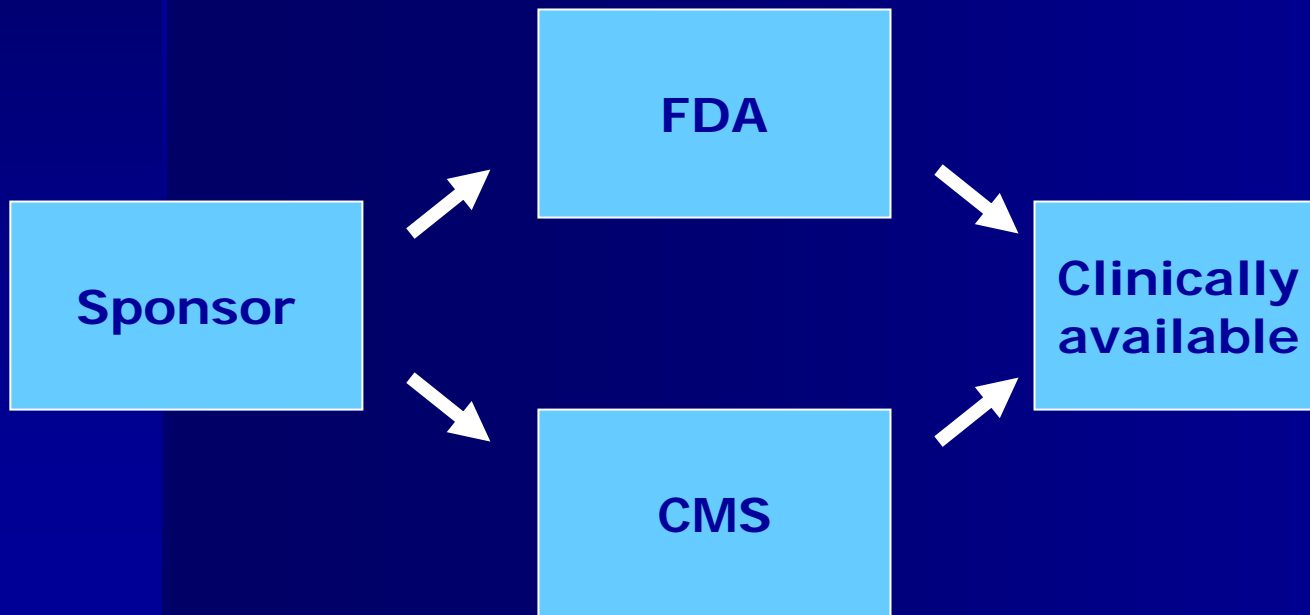


Time

DHHS/FDA/CDRH

# New Paradigm

- Early involvement of CMS can expedite time to market
- *Parallel* process



Time