From DES to Percutaneous Valves: What Interventional Doctors Need to Know about Regulatory Barriers and Solutions to Global Device Evaluation

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Duke University Medical Center

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Special Government Employee

Circulatory Devices Advisory Panel

U.S. FDA

Co-Director

Cardiac Safety Critical Path Initiative

Founder, Co-Director

Japan-USA Harmonization By Doing Program

Member, U.S. FDA Team

GHTF Study Group 5

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Special Report

Drug-Eluting Stents "Deliver Heartburn"

How Do We Spell Relief Going Forward?

Mitchell W. Krucoff, MD; Ashley Boam, MSBE; Daniel G. Schultz, MD

"Breakthrough" technologies may produce rare or unexpected performance issues in postmarket use, especially when rapid market penetration into large patient populations outpaces the development of clinical knowledge. Although high-profile meetings or news media coverage may help draw attention to such issues, ultimately it is careful scientific

organizations, and academics are to be applauded for collaborative efforts to continue to collect and provide unbiased access to new and extended patient-level data, and several leading peer-reviewed journals have expedited publication to facilitate dissemination of these findings. For example, 7 articles on DES outcomes were included in the March 8

Krucoff et al, *Circulation*. 2007.

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In Premarket

Sanket S. Dhruva, MD
Lisa A. Bero, PhD
Rita F. Redberg, MD, M

Medical-Devices Sector Could Face Tougher Regulatory Pathway

Article

By Jon Kamp
Of DOW JONES NEWSWIRES

As the Food and Drug Administration reviews the way it approves medical devices, companies are girding for changes that could make it tougher and more expensive to roll out new products.
The FDA, under its new leadership, has toughened its image. Amid this atmosphere, device makers are particularly focused on a review of a fast-track approval pathway known as 510(k) that has drawn criticism

Jon Kamp, Dow Jones Newswires; 617-654-6728; jon.kamp@dowjones.com

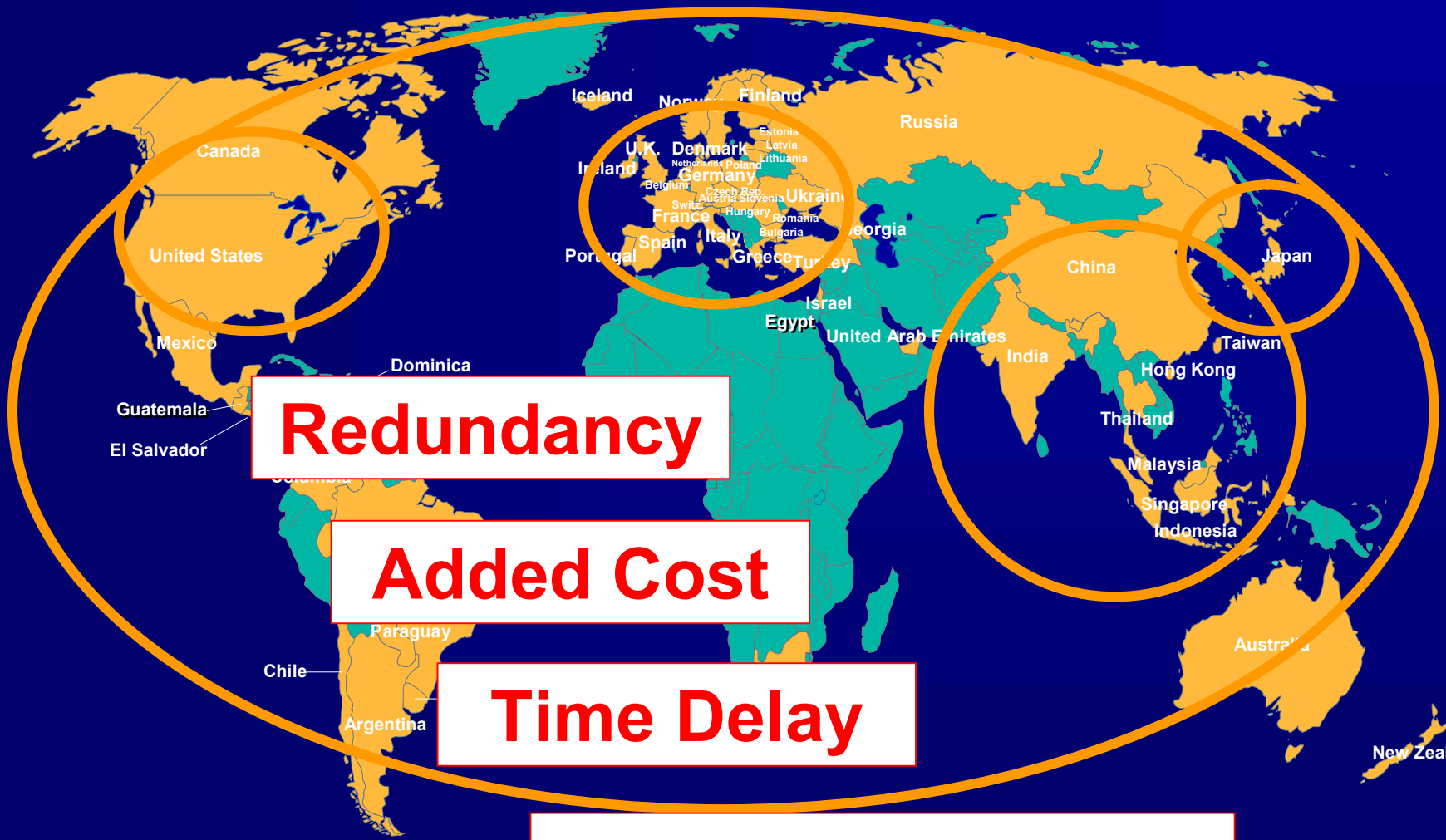
New Device Regulations: Why Should Doctors Care?

- ***Health Care Access***
  - Device "lag"
- ***Economy***
  - Health care cost
  - Revenue from & for competitive innovation
- ***Patient information***
  - Safety: risks vs. benefits of implants
- ***Unique options for professional collaboration:***
  - Shared experience, priorities & needs across all stakeholders (patients, academics, industry, regulatory)
- ***More informative trial designs:***
  - Regulatory focus on public health not just marketing
  - Better trials support innovation

New Device Innovation:
Lots Going On, But One Approach Does Not Fit All

- New & bioabsorbable DES
- Percutaneous mitral valves
- Percutaneous aortic valves
- STEMI adjunct devices
- LVAD/artificial hearts
- And more!

Global Clinical Evaluation



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October 2002

International Cardiovascular Disease & Therapy: *Are We More Alike or Different?*

Regulatory Perspective

- ***Epidemiology*** :
  - disease prevalence
  - natural history
  - risk
- ***Relevance:***
  - clinical practice patterns
- ***Genetics:***
  - Metabolism
  - Metabolites
- ***Poolability:***
  - data quality
  - follow up

Racial CV Therapy History

- ***Drugs:***
  - Dose response
  - Toxicities
- ***Devices:***
  - Body size
- ***Subgroups > Race***
  - Age
  - Gender
  - Diabetes

FDA Perspectives: 1997-2010

1997: Food & Drug Modernization Act (FDMA):

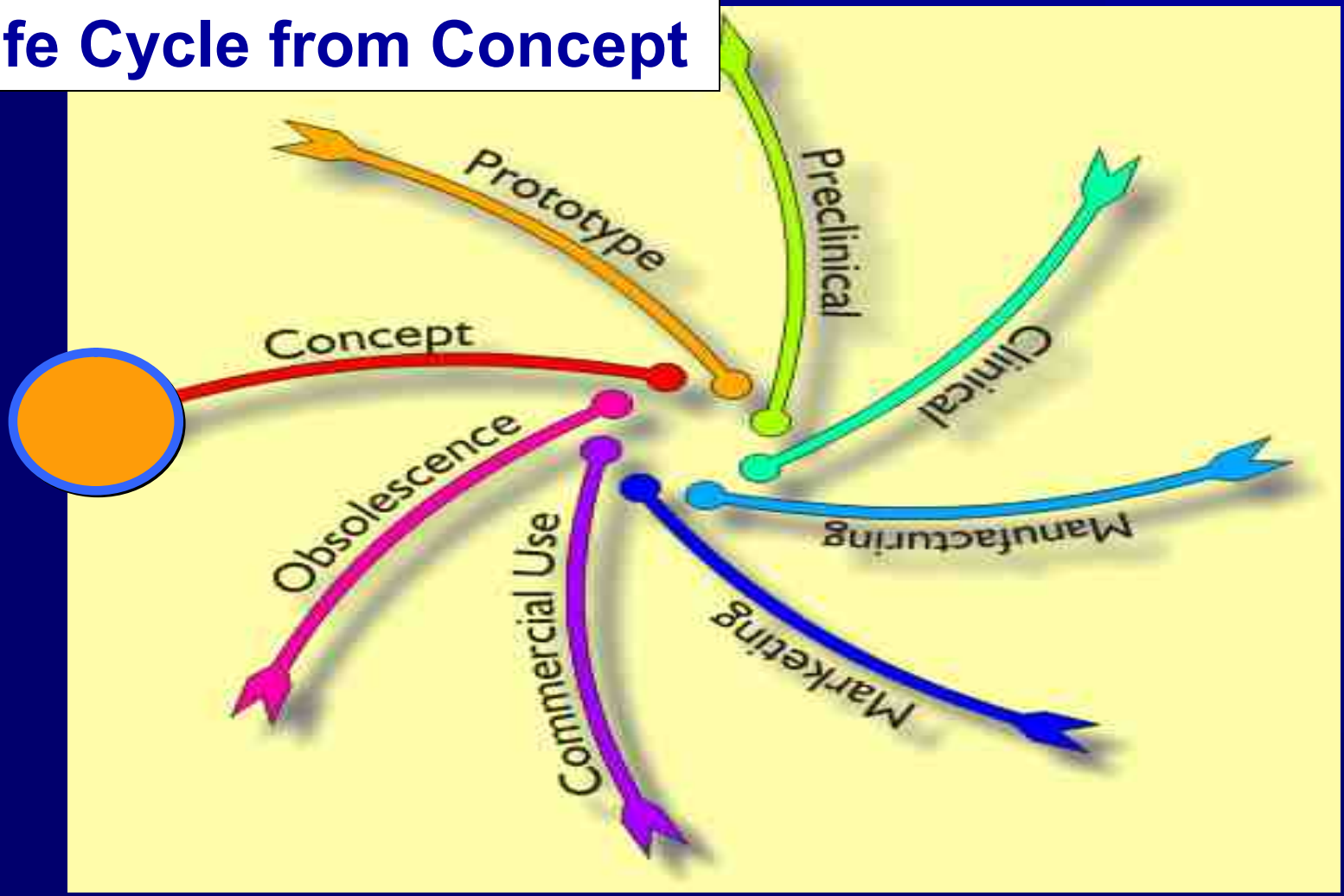
Pre-IDE dialogue

"Least Burdensome"

Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

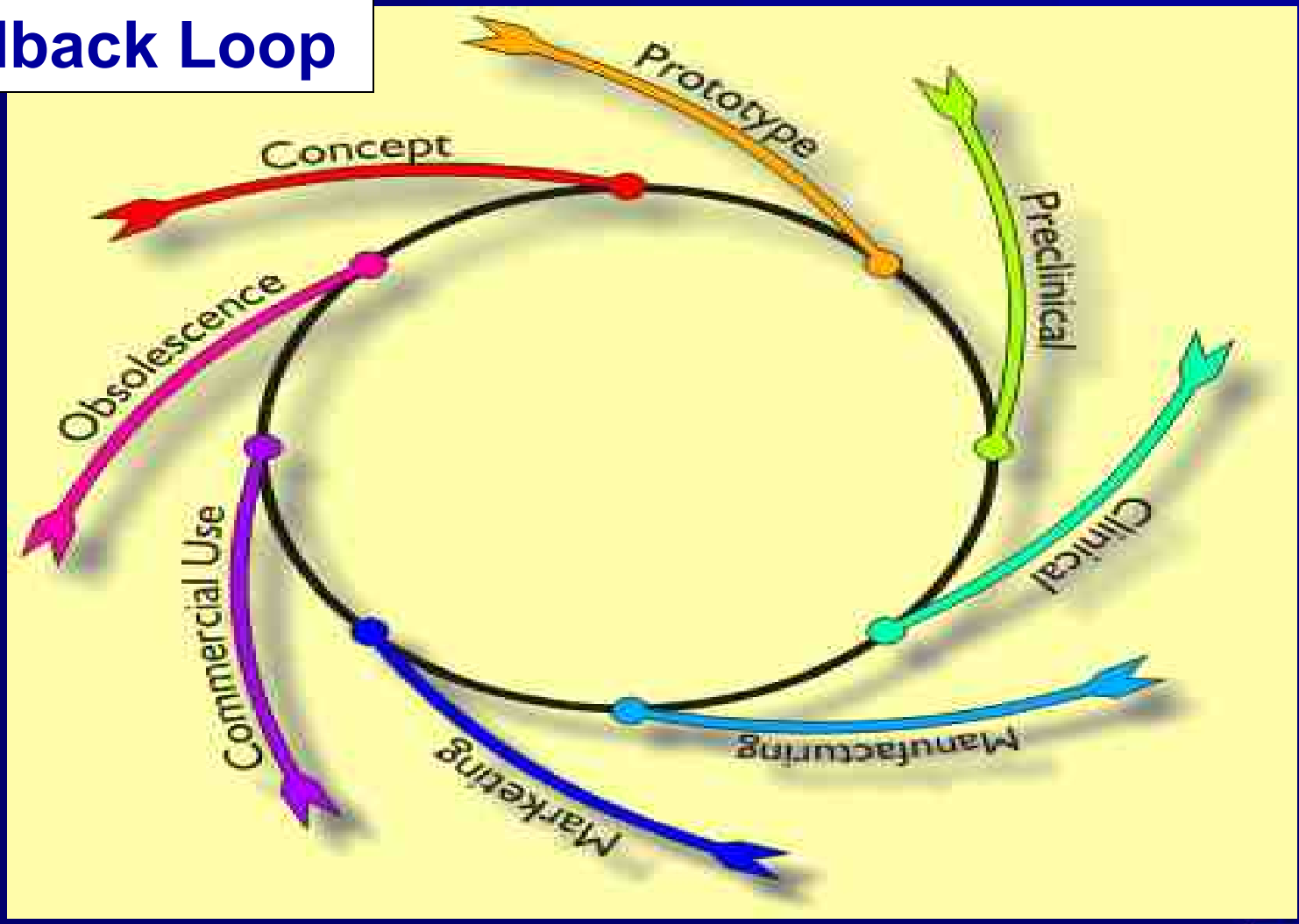
Life Cycle from Concept



Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

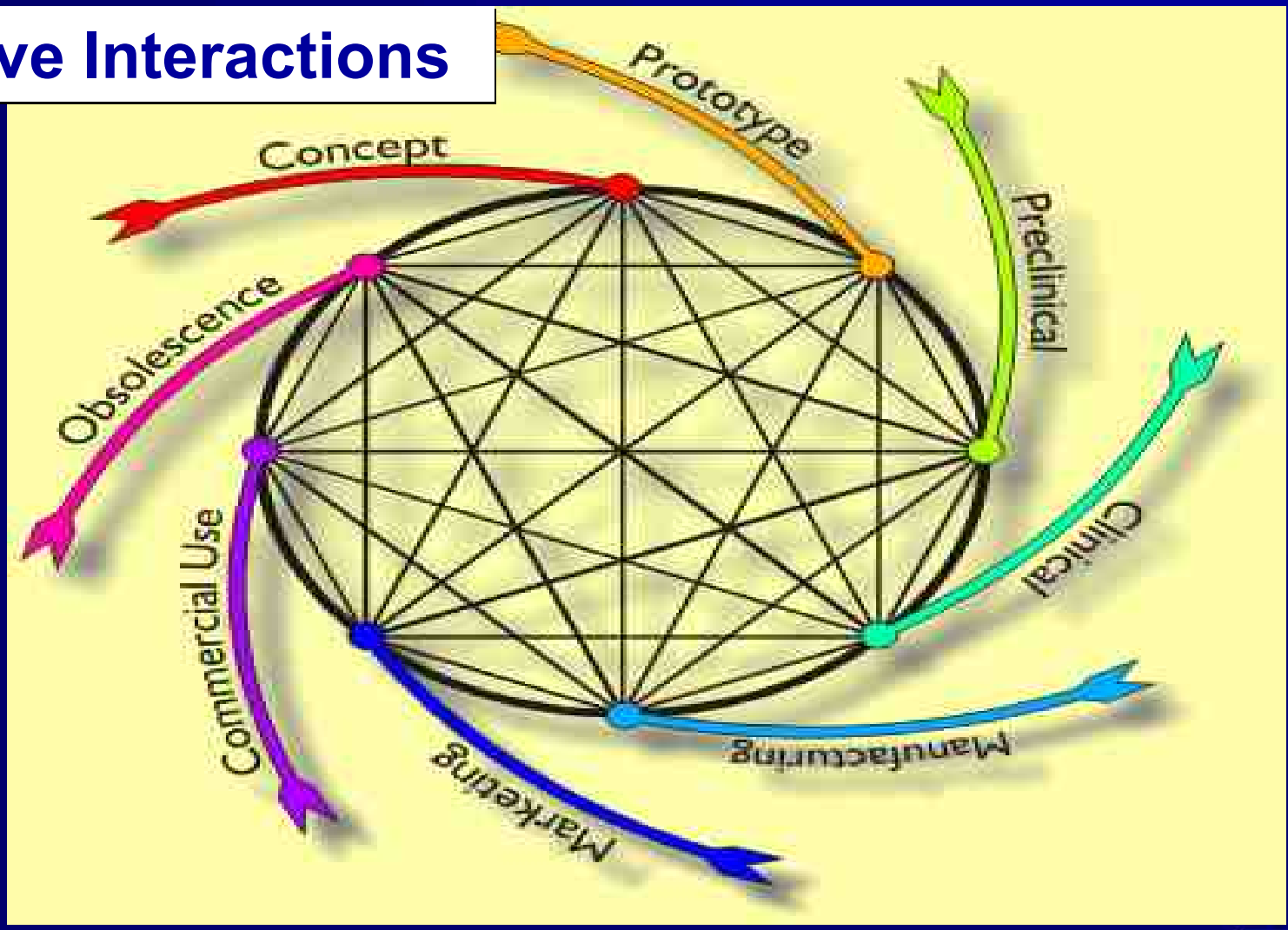
Feedback Loop



Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

Iterative Interactions



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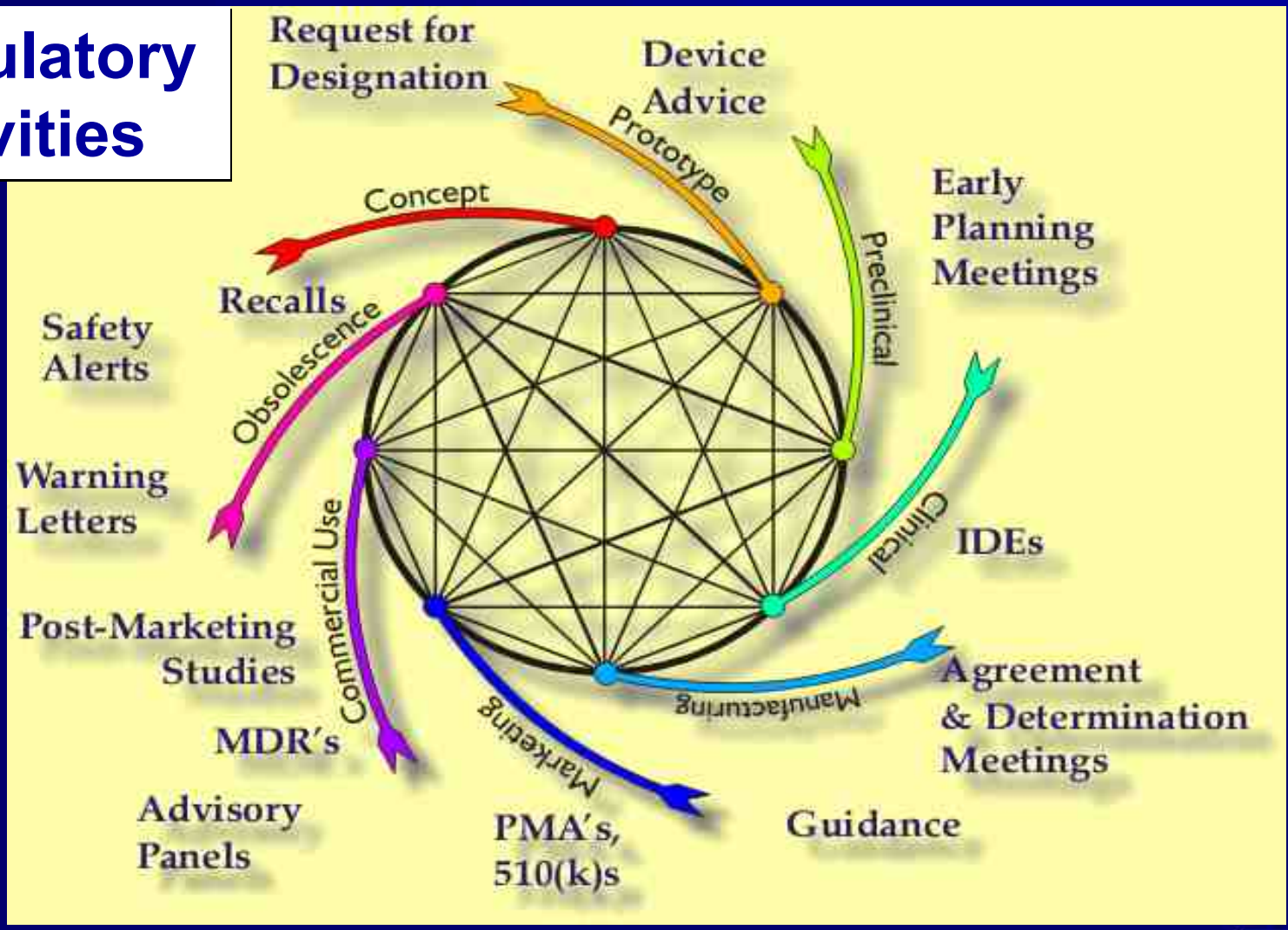
Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

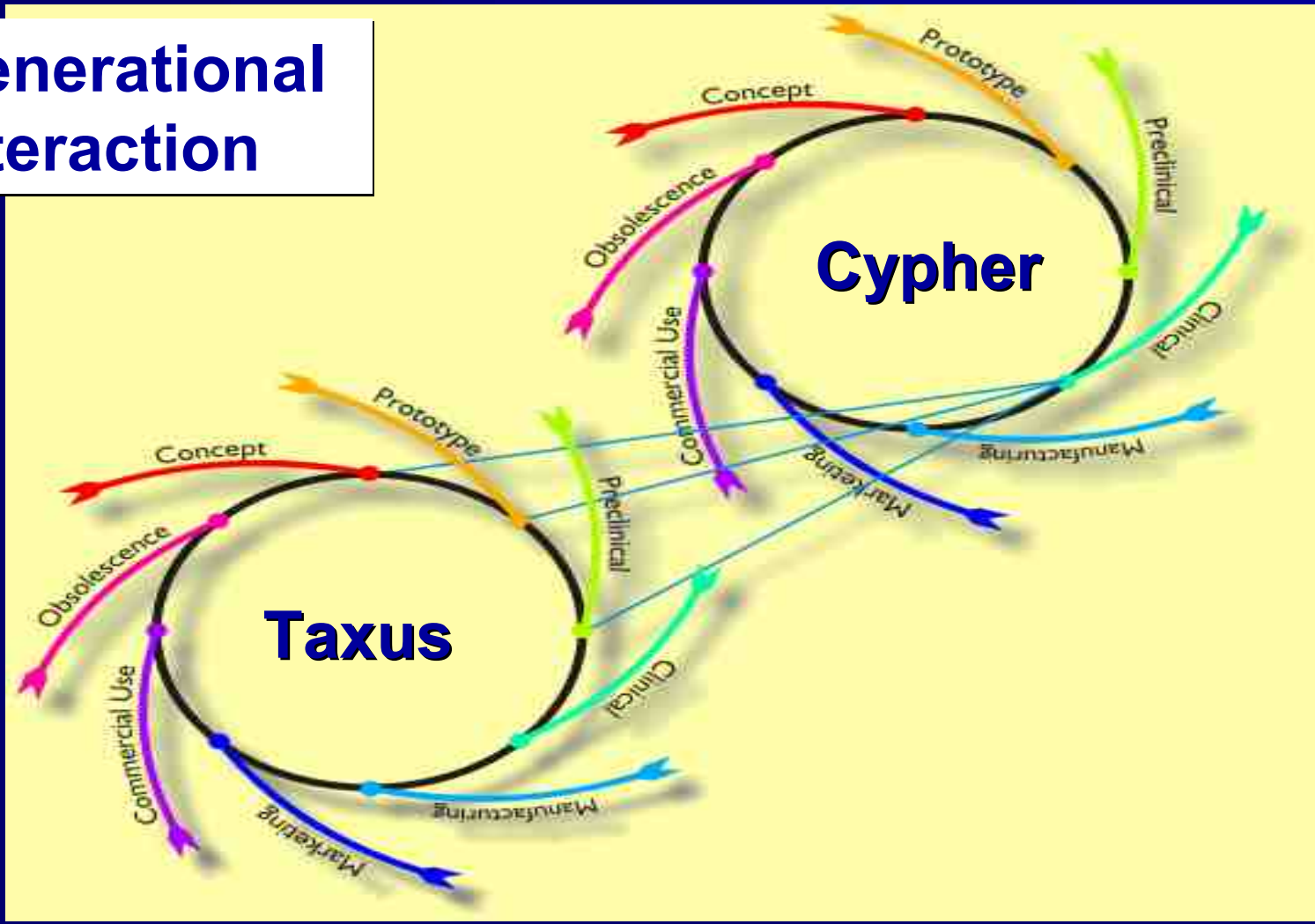
Regulatory Activities



Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

Generational Interaction



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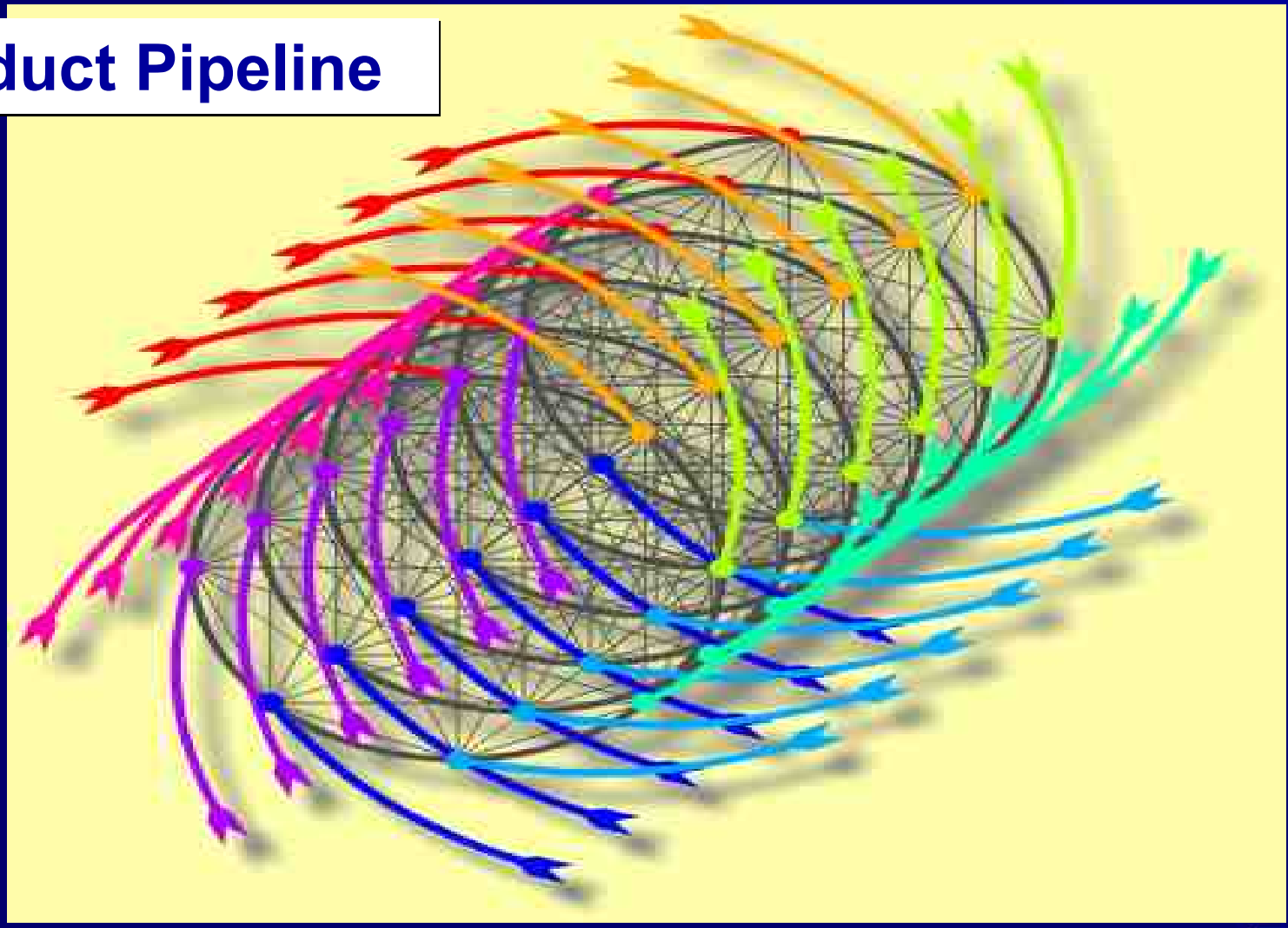
Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

Product Pipeline



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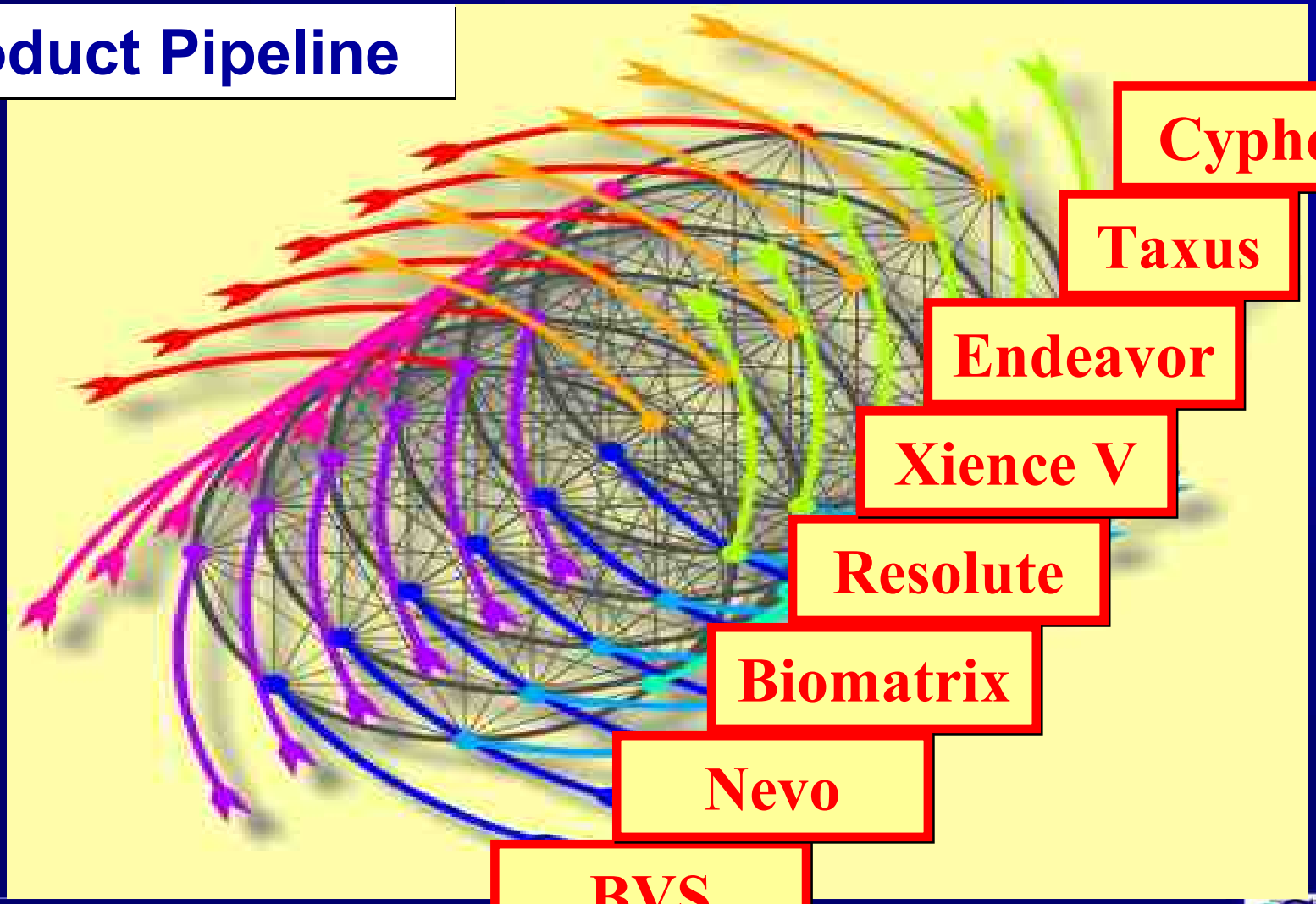
Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle

Product Pipeline



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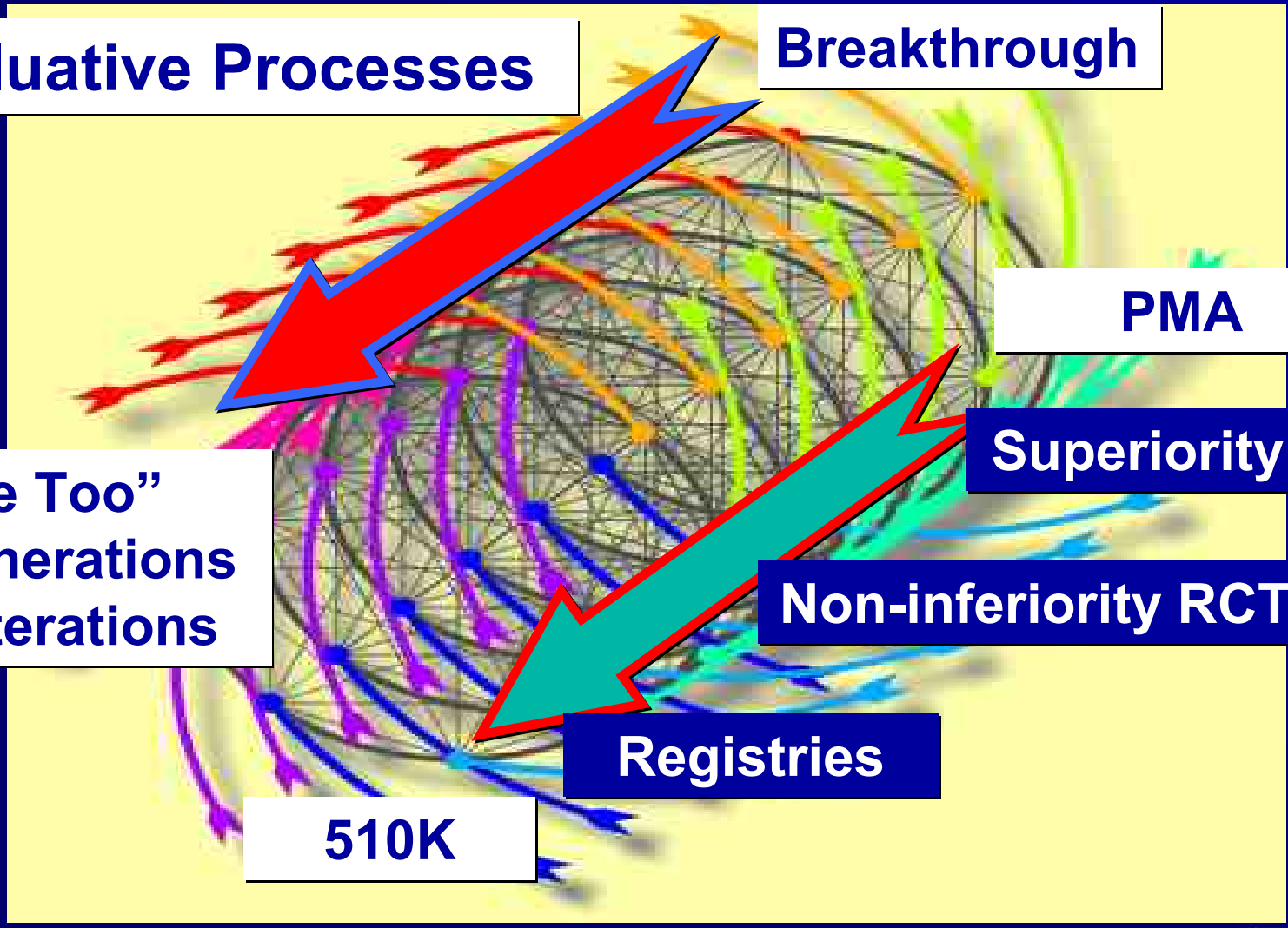
Regulatory Issues in Cardiovascular Devices

Total Product Life Cycle



What's New in FDA DES Perspectives: *1997-2010*

1997: Food & Drug Modernization Act (FDMA):

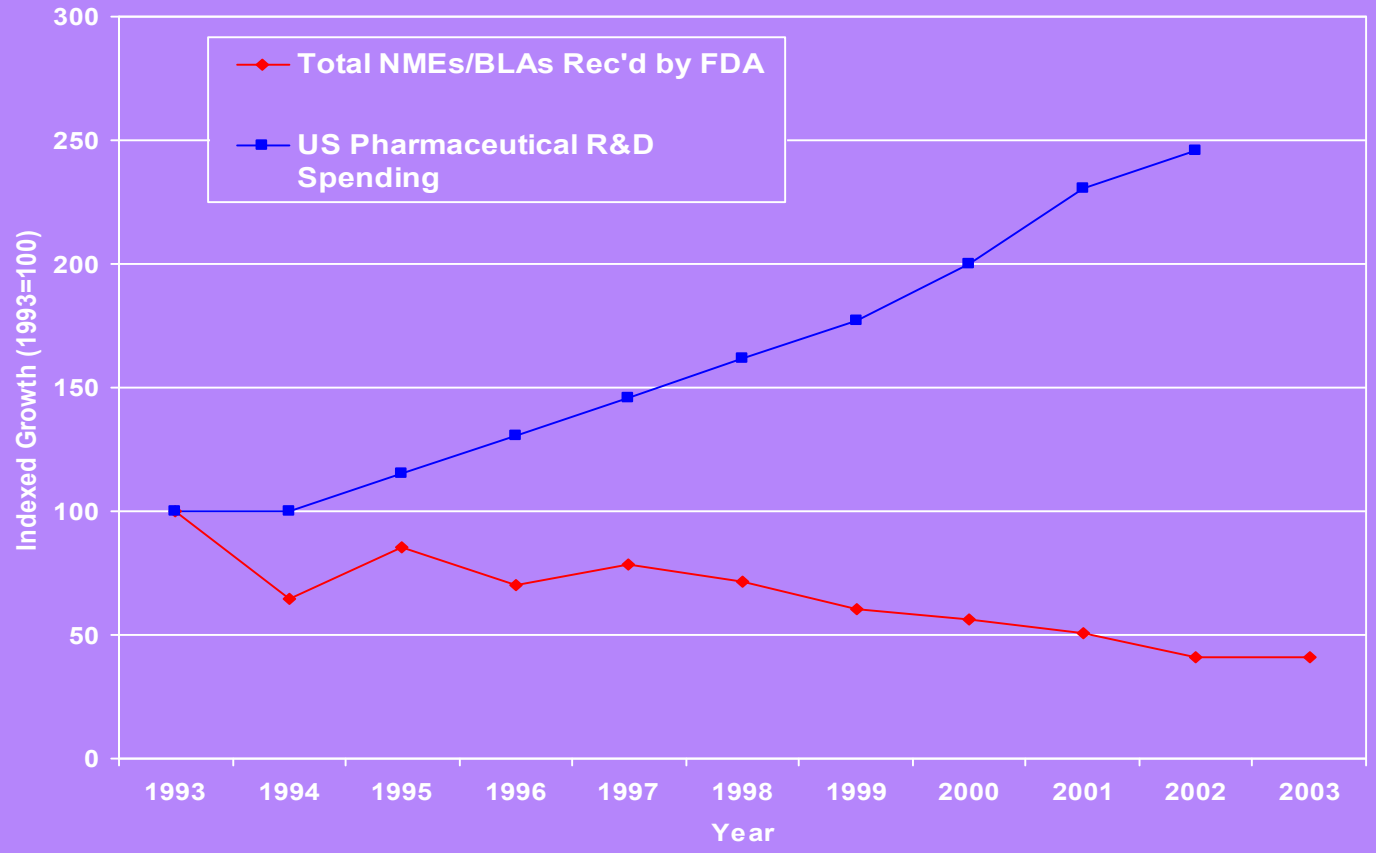
Pre-IDE dialogue

"Least Burdensome"

Pre-market "reasonable assurance of safety & effectiveness"

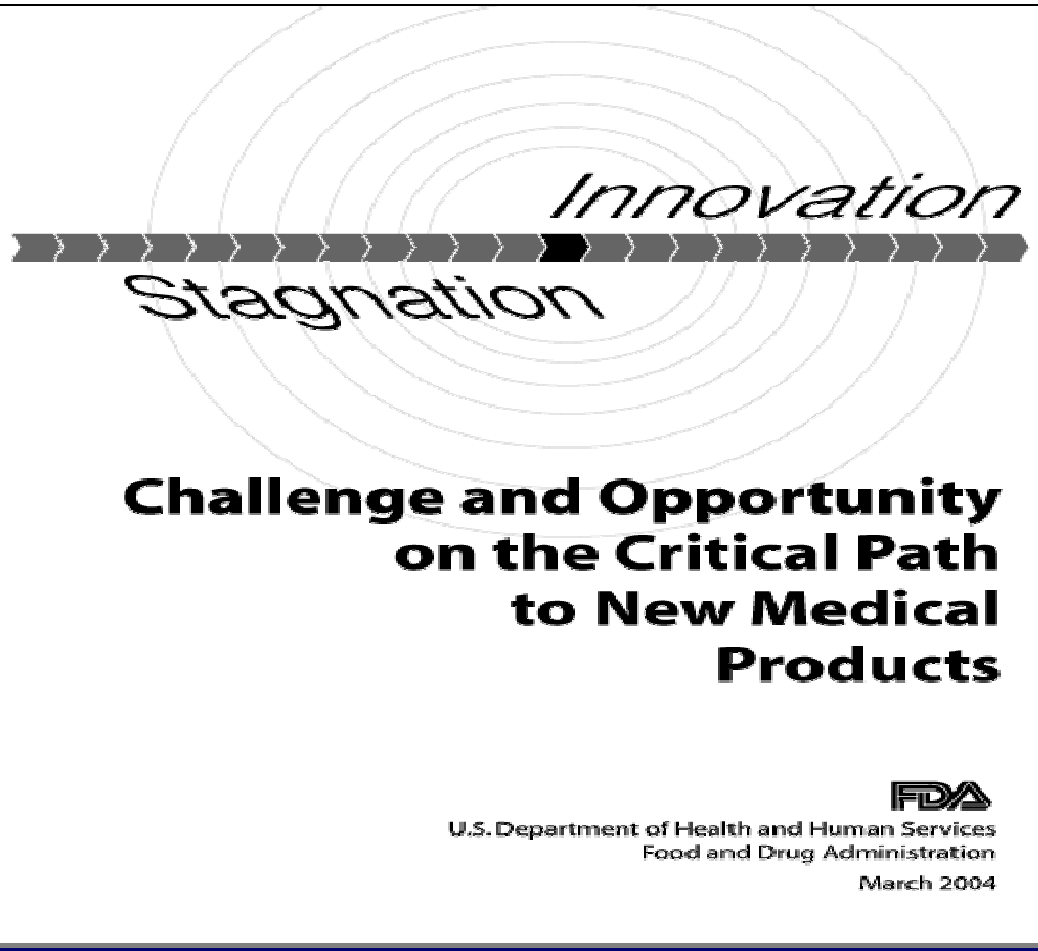
Rising Costs, Slowing Innovation

Trends in R&D Spending vs. New Approvals



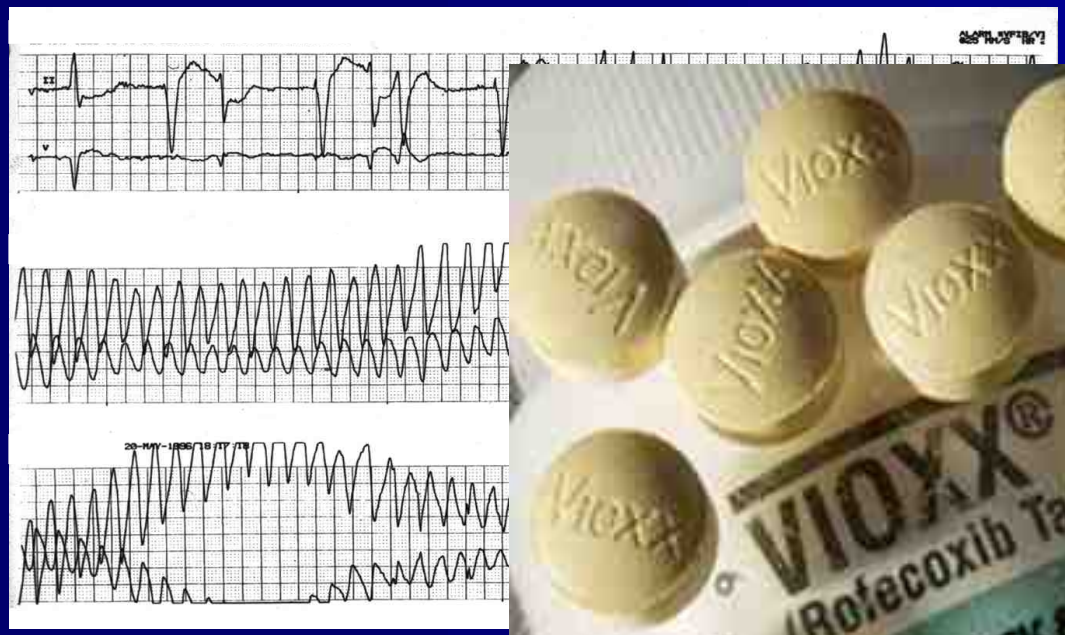
Critical Path Initiatives: March 2004

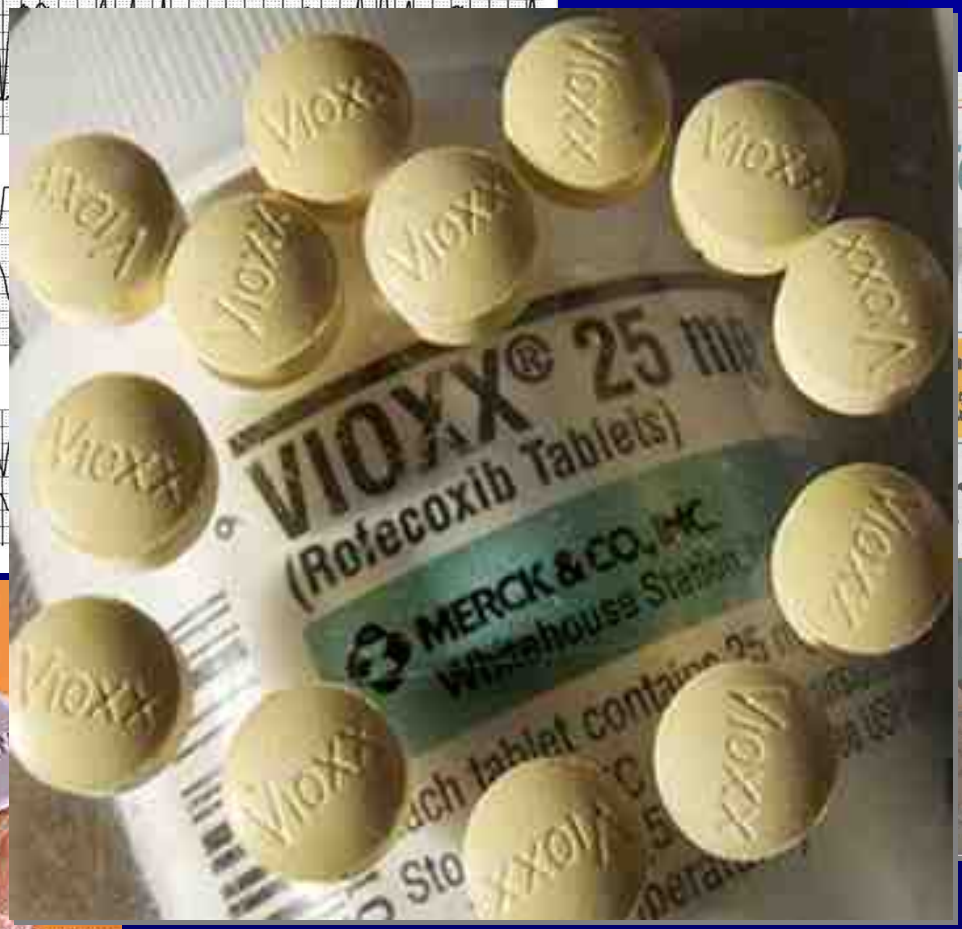
http://www.fda.gov/oc/initiatives/criticalpath/

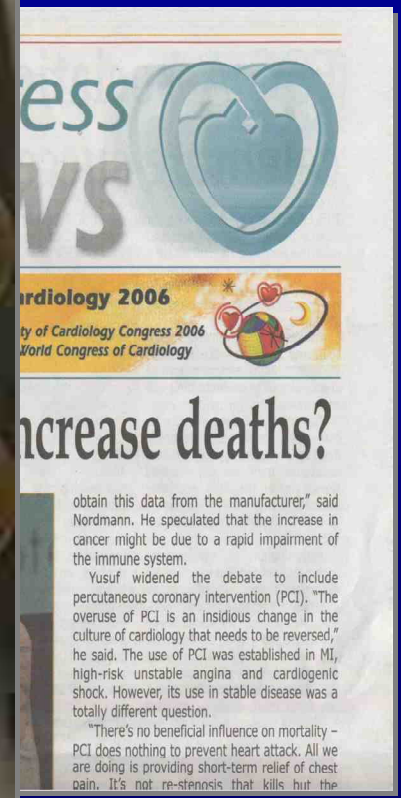


Cardiac Safety:

Evaluating rare but catastrophic events.







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CARDIAC SAFETY www.cardiac-safety.org

2006 FDA – Duke/DCRI Memorandum Of Understanding (MOU)

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

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FDA News

FOR IMMEDIATE RELEASE
P06-147
September 27, 2006

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888-INFO-FDA

FDA and Duke Clinical Research Institute Form Partnership to Collaborate on Cardiac Safety Virtual

Cardiac Safety Research Consortium

(CSRC)

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Medical Product Development Strategy Consensus White Papers

Progress in Cardiology

ELSEVIER AHJ American Heart Journal

Cardiac Safety Research Consortium Conference Papers

New precompetitive paradigms: Focus on cardiac safety

John Finkle, MD,[a] Daniel Bloomfield, MD,[b] Kathleen Uhl, MD,[c] Wendy Sanhai, PhD,[d] Norman Stockbridge, MD,[e] and Mitchell W. Krucoff, MD[f]

For the last several years, there have been a decreasing number of new innovative medical therapies approved for use in the United States despite an increasing expenditure on medical product development.[1,2] This situation has been compounded by an increasing awareness

medical device development. By sharing data across industry, academia, and government agencies, large exploratory research projects of mutual interest become feasible because the costs can be shared. The research will be published and made available for

CSRC: *Thinktank/Incubator 'Signature" Programs*

- Collect expertise
- Share ideas
- Produce white papers

Beyond thinktanks: Incubator environments to mobilize unique public health interest collaborations related to cardiac safety

TUESDAY

ESC Congress News

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WORLD HEART FEDERATION®

World Congress of Cardiology 2006

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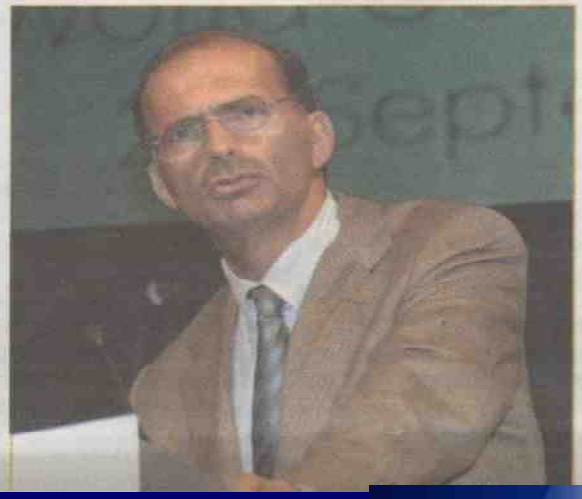
Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

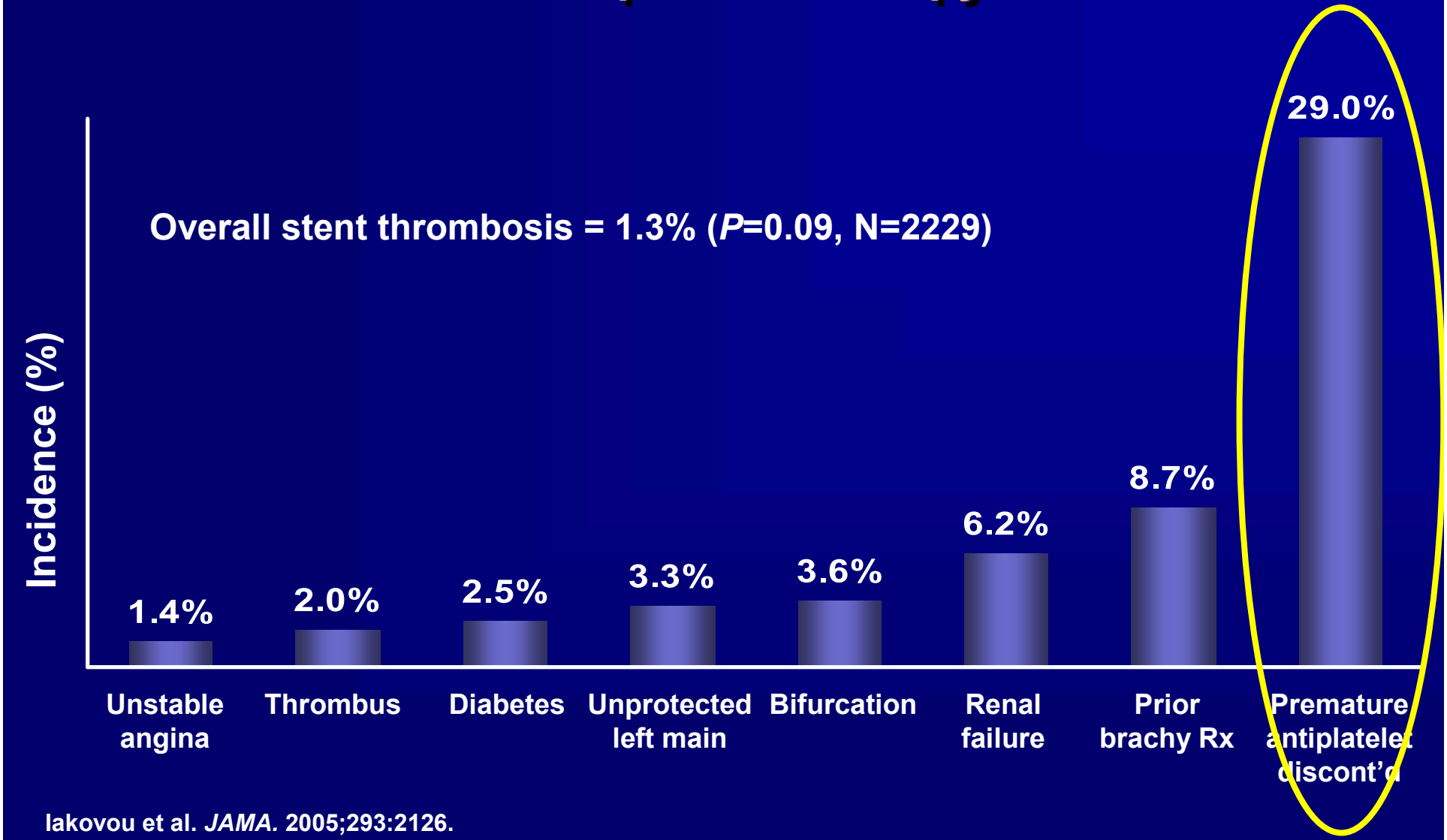


obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the

Discontinuation of Anti-platelet Therapy and Risk for ST



Iakovou et al. *JAMA.* 2005;293:2126.

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DES Thrombosis: A Novel Regulatory Domain: Obligatory Drug-Device Safety Interaction

- ***DES:***
  - Combination drug-on-device (Medical Device Reg)
  - Studied in de-novo 1-vessel PCI to reduce restenosis
- ***Clopidogrel/Prasugrel:***
  - Thienopyridines (Drug Reg)
  - Studied in ACS patients
- ***Public health issue:***
  - Crossover of drug-device “cultures”
  - No clear regulatory predicate
  - Combinations of new DES and new DAP
  - Post-market “real world” population

CSRC
Obligatory Drug-Device Safety Research Programs

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DES & Extended Dual Antiplatelet Therapy:
February 2007, April 2007, September 2007

Regulatory

- FDA:
  - CDER
  - CDRH
  - Off Comm
- E.U.
  - Austria
  - U.K.
  - Sweden
- Japan:
  - MHLW
  - PMDA

Academia

- Duke
- Harvard
- Cleveland Clinic
- Columbia
- U of NM
- Wash Hrt Ctr
- London School of Hyg & Trop Med
- CVPath

Societies

- ACC
- SCAI
- ESC

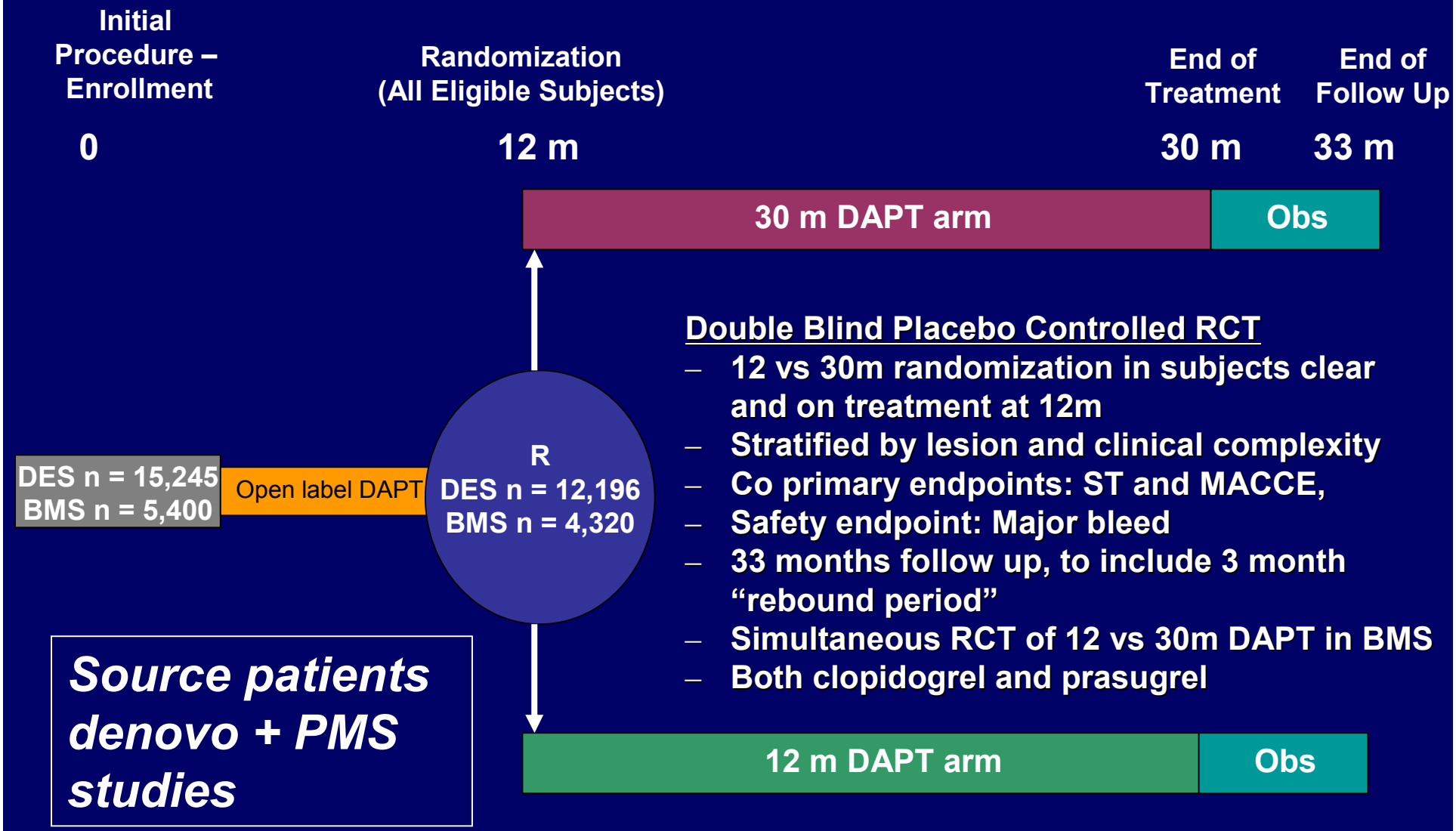
Federal

- NIH
- AHRQ

Industry

- Abbott
- Medtronic
- BSCI
- Cordis/J&J
- Biosensors
- OrbusNeich
- Eli Lilly (Daichi)
- Sanofi
- BMS

Dual Antiplatelet Therapy (DAPT) RCT



Double Blind Placebo Controlled RCT

- 12 vs 30m randomization in subjects clear and on treatment at 12m
- Stratified by lesion and clinical complexity
- Co primary endpoints: ST and MACCE,
- Safety endpoint: Major bleed
- 33 months follow up, to include 3 month "rebound period"
- Simultaneous RCT of 12 vs 30m DAPT in BMS
- Both clopidogrel and prasugrel

Source patients denovo + PMS studies

Excess Dosing of Antiplatelet and Antithrombin Agents in the Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes

Karen P. Alexander, MD
Anita Y. Chen, MS

Context Effective medical care assumes delive
propriate patients with doses comparable to th

Potency or Low Bleeding:

- ❑ Thienopyridines
- ❑ Anti-coagulants
  - ❑ *unfractionated heparin*
  - ❑ *LMWH*
  - ❑ *direct thrombin inhibitors*
- ❑ IIbIIIa inhibitors
- ❑ Novel anti-platelet inhibitors
- ❑ ASA

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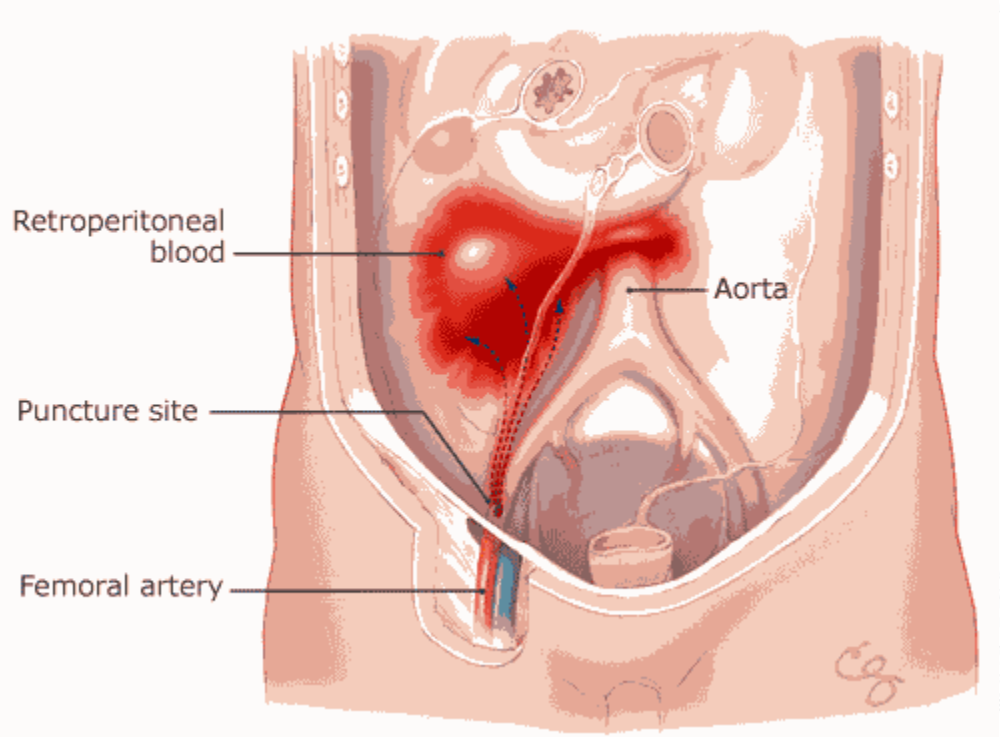

by 3 age groups (<65 years, 65-74 years, and ≥75 years), P<.001 for all 3 treatment groups. Standard errors are all less than 1.5%. Numbers provided are the individuals receiving treatment with available dos tion in each age group.

Source: Alexander, K, Chen A, Rowe M, et al JAMA Dec. 28, 2005 Vol 294, No. 24

Shifting the Balance of Potency and Bleeding Risk for Anti-Coagulant and Anti-Platelet Agents Through Radial Arteriotomy:

An Obligatory Drug-Device Safety Interaction Cardiac Safety Critical Path Thinktank/Incubator

23-June, 2010
Washington D.C.
FDA Headquarters

With intellectual and program planning support from the (alphabetical) Academic Research Consortium (ARC), the American College of Cardiology (ACC), the Cardiac Safety Research Consortium (CSRC), the Duke Clinical Research Institute (DCRI), the Society of Coronary Angiography and Intervention (SCAI) and the United States Food and Drug Administration (FDA).

- Cleveland Clinic
- Columbia University
- Duke University
- Harvard
- Johns Hopkins
- Washington Heart Ctr
- U.S. FDA
- AHRQ
- NIH
- ACC
- SCAI
- SOLACI
- ESC

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GHTF
1992 - 2010
Global Harmonization Task Force
Working Towards Harmonization
in Medical Device Regulation
About GHTF
Steering Committee
Study Groups
GHTF Documents
Meetings & Training
Liaison B
GHTF > Study Groups
Study Groups
Global Harmonization Task Force (GHTF) Study Groups are est
address premarket through postmarket medical device issues.
Study Group 1 - Premarket Evaluation
Study Group 2 - Post-Market Surveillance/Vigilance
Study Group 3 - Quality Systems
Study Group 4 - Auditing
Study Group 5 - Clinical Safety/Performance
Need for human studies
Pre-market
Post-market
Modality for intellectual convergence
Pragmatic focus
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FDA U.S. Food and Drug Administration — Department of Health and Human Services

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative

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Phone: 919-660-9461
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PMDA OIP Director and Duke Professor Named First Co-Directors of Japan-USA Harmonization By Doing Program

DURHAM, NC (March 10, 2010) – Reflecting a significant step forward in operating structure, the Japan-USA Harmonization By Doing (HBD) program announced the organization's first co-directors: Toshiyoshi Tominaga, Ph.D., director of the Office of International Programs (OIP) of Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and Mitchell W. Krucoff, M.D., professor of cardiology at Duke University Medical Center and director of the Cardiovascular Devices Unit for the Duke Clinical Research Institute (DCRI).

The “Collaborative Scheme” for parallel medical device development

U.S. Department of Health & Human Services www.hhs.gov

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Medical Devices

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Device Advice: Device Regulation and Guidance

International Information (Medical Devices)

- Important New Changes to Canadian Regulatory Quality Systems Requirements
- Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative
- Contacts

Japan - U.S. "Harmonization By Doing" HBD Pilot Program Initiative

ANNOUNCEMENT (June 23, 2009): U.S. – Japan Pilot Program Regarding Medical Device Collaborative Consultation and Review of Premarketing Applications

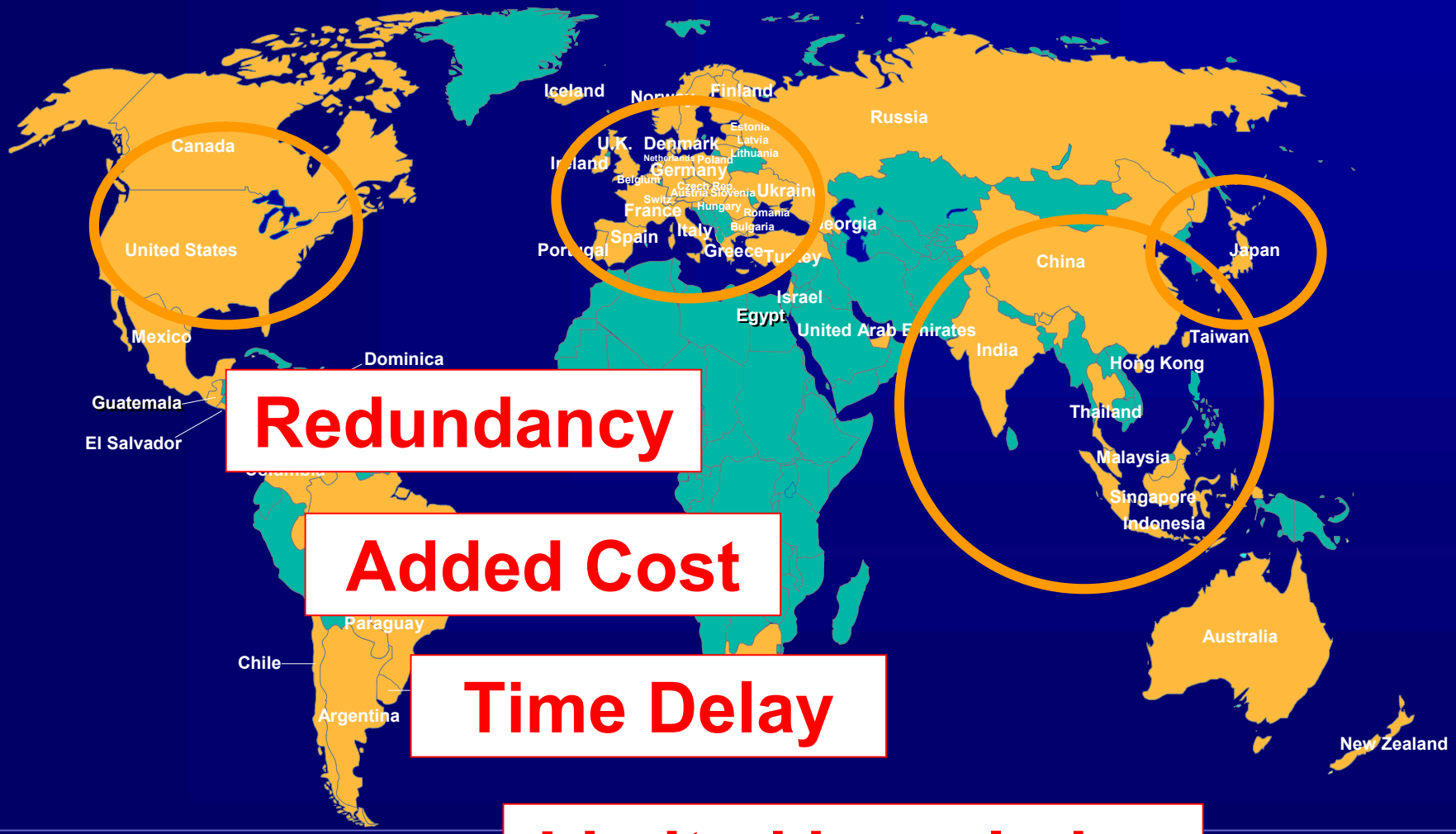
Japan MHLW/PMDA and U.S. FDA announced this week the launch of a bilateral pilot program on collaborative consultation and review of new cardiovascular devices. The goal of the pilot program is to advance both the speed and quality of clinical/statistical consultations and the regulatory review process for potential earlier market access and improved public health benefit. This collaboration would permit the scientific review staff of both MHLW/PMDA and FDA to discuss the contents of an individual submission in order to gain valuable regulatory information pertaining to device development and clinical trial design.

The Collaborative Scheme is one of several focused topics that will be discussed at the upcoming Japan-US Harmonization By Doing (HBD) West 2009 Meeting, July 16-17 at the FDA White Oak Campus.

- FDA announcement (English)
- MHLW announcement (*tsuchi*) (Japanese)

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/InternationalInformation/ucm053067.htm

Clinical Evaluation of New Medical Devices



Duke Clinical Research In
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October 2002

Global Clinical Evaluation

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October 2002

Conclusions: FDA Regulatory Perspective
Why Should Doctors Care?

- Regulatory processes need clinical insight to better serve the public health
- The more the scientific mission of professional societies, regulatory authorities and manufacturers is the same—to provide quick access to better, safer therapies—the "less burdensome" to all.

Conclusions: FDA Regulatory Perspective
Why Should Doctors Care?

- Patients & patient care
- Economy
- Technical insights
- Professional (global) collaborations
- More efficient, informative clinical trials science

Innovations In Interventional Cardiology: The U.S Perspective (FDA Perspectives on Device Approval)

Mitchell W. Krucoff MD, FACC

Professor of Medicine / Cardiology

Duke University Medical Center

Director, Cardiovascular Devices Unit

Duke Clinical Research Institute

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