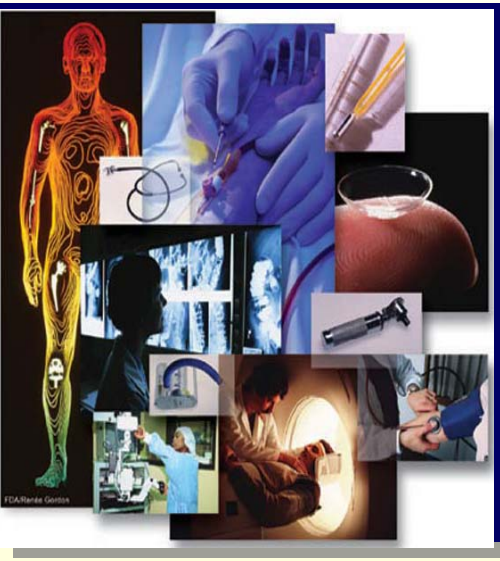


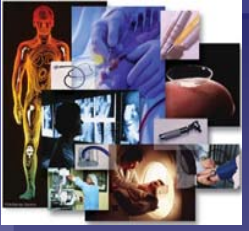
Medical Device Regulation in the U.S.:
A Risk-based Model

Larry Kessler, Sc.D.

Director, Office of Science and Engineering Laboratories

Center for Devices and Radiological Health
U.S. Food and Drug Administration

Asian Harmonization Working Party, October 2007

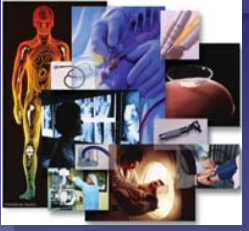


Our Mission

Getting safe and effective devices to market as quickly as possible...

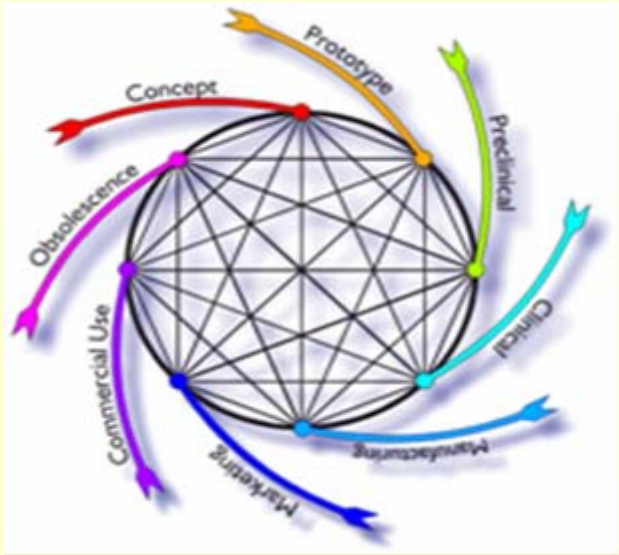
... while ensuring that devices currently on the market remain safe and effective.

Helping the public get science-based accurate information about medical devices and radiological products needed to improve health



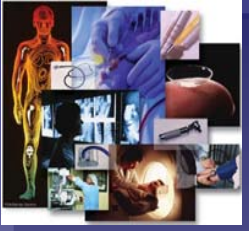
"Total Product Life Cycle" Vision

Efficient, Effective, and Predictable Product Development



Ensuring the Safety of Marketed Medical Devices

Enabling Technology and Innovation



CDRH's Legislative Mandates

1968 Radiation Control for Health & Safety Act (RCHSA)

1976 Medical Device Amendment of 1976

1988 Clinical Laboratory Improvement Amendments (CLIA)

1990 Safe Medical Devices Act (SMDA)

1992 Mammography Quality Standards Act (MQSA)

1992 Medical Device Amendments

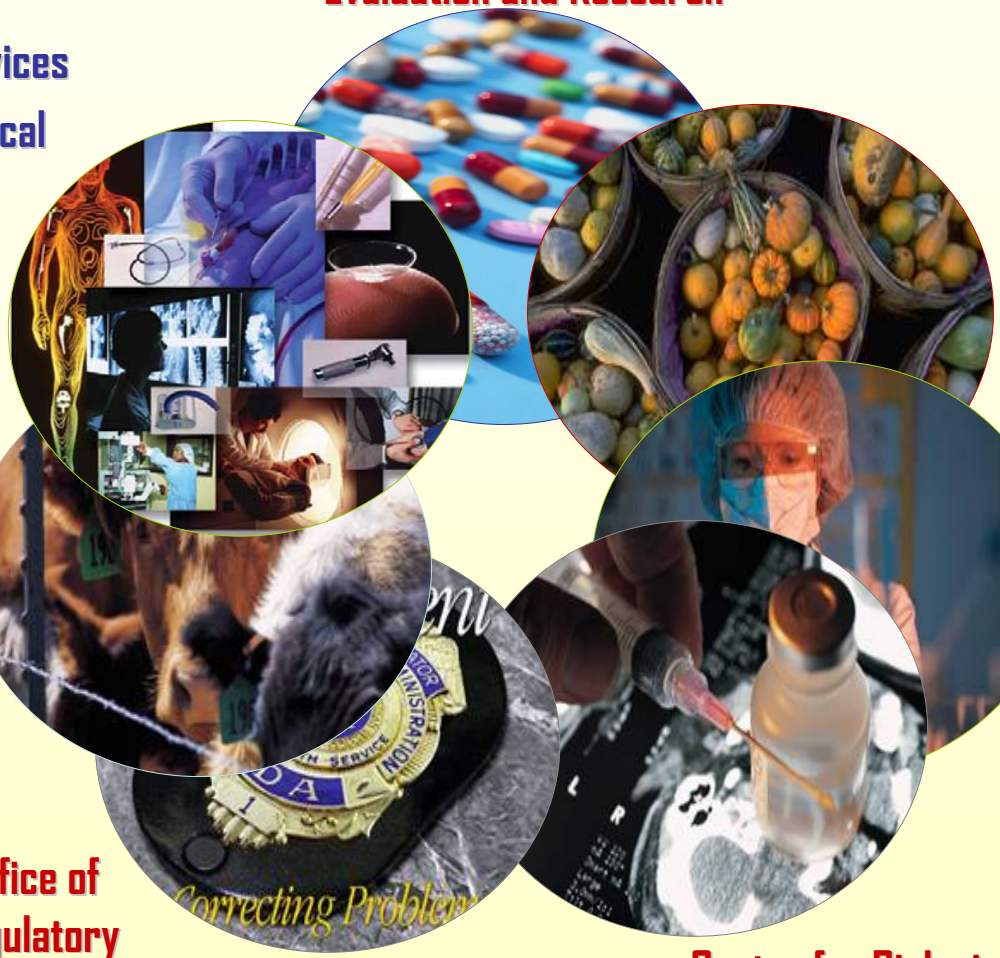
1997 Food & Drug Administration Modernization Act (FDAMA)

2002 Medical Device User Fee and Modernization Act (MDUFMA)

2005 Medical Device User Fee Stabilization Act (MDUFSA)

2007 FDA Amendments Act of 2007 (FDAAA)

U.S. Food and Drug Administration



Center for Drug Evaluation and Research

Center for Devices and Radiological Health

Center for Food Safety and Applied Nutrition

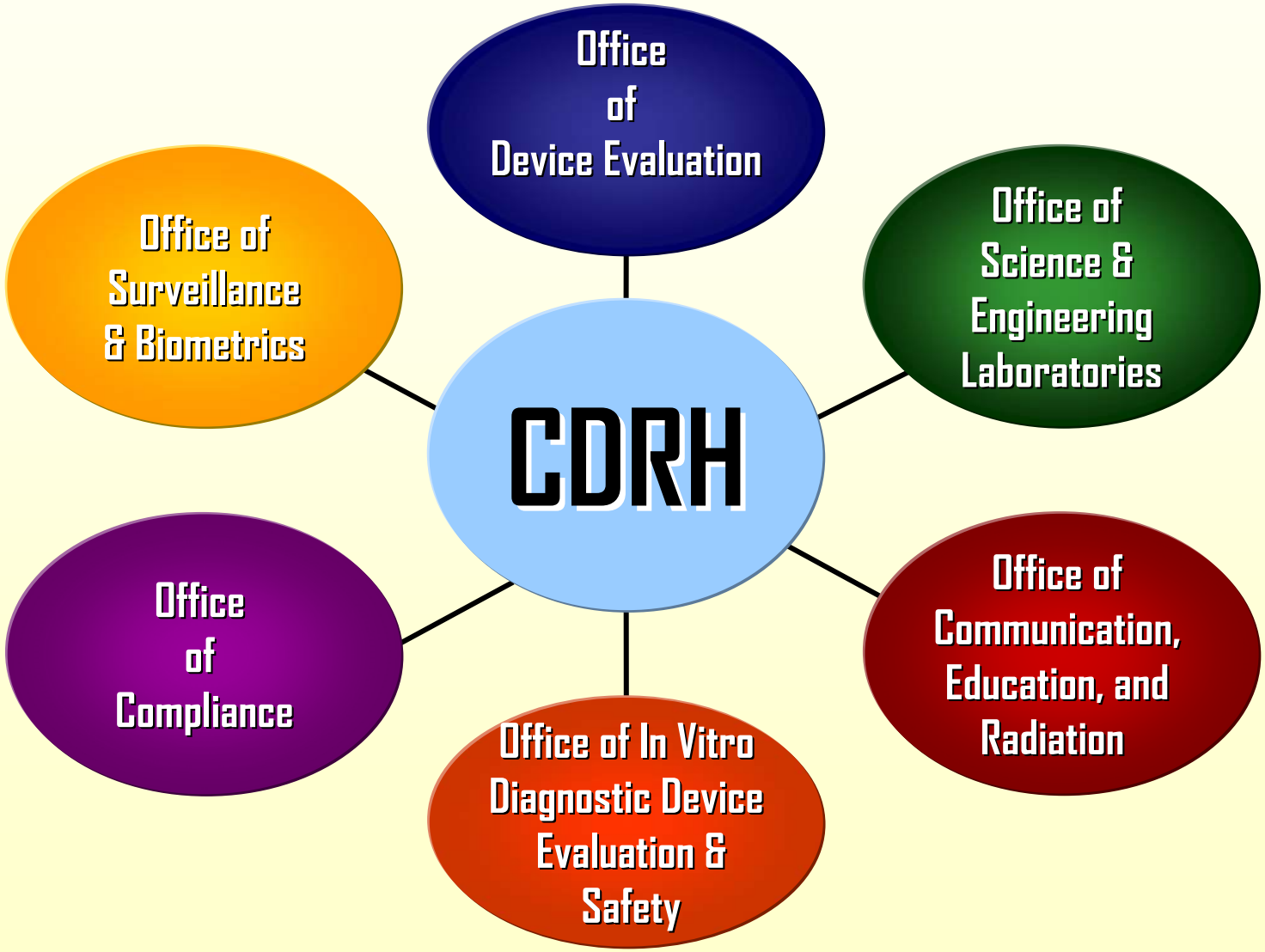
Center for Veterinary Medicine

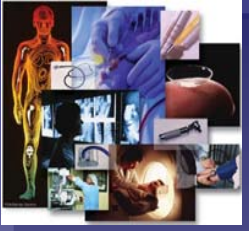
National Center for Toxicological Research

Office of Regulatory Affairs

Center for Biologics Evaluation and Research

Center For Devices and Radiological Health





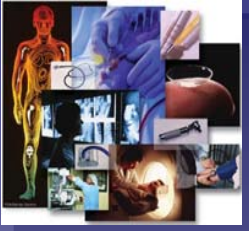
Medical Device

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

1. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or
2. intended to affect the structure or any function of the body of man,

and which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

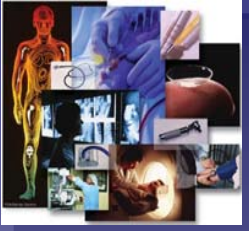
Section 201, Food Drug and Cosmetic Act



Safety

"There is reasonable assurance that a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks."

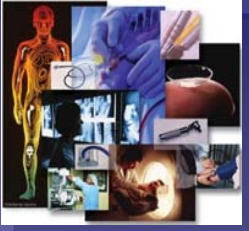
21 CFR 860.7



Effectiveness

"There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that 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."

21 CFR 860.7

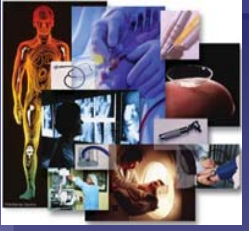


Valid Scientific Evidence

"The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations..."

"...evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can be fairly and responsibly concluded by qualified experts that there is a reasonable assurance of safety and effectiveness of a device under its conditions of use."

21 CFR 860.7

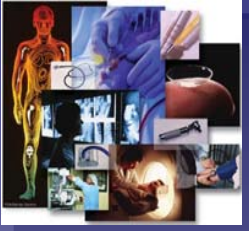


Elements of FDA Regulatory System

- **Premarket controls and review**
- **Quality systems requirements**
- **Postmarket Surveillance**
- **Laboratory investigations**
- **External Communication**
- ***New legislation and regulations***

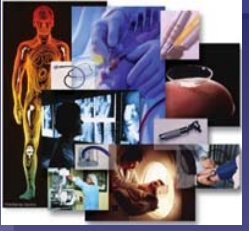
Risk-Based Paradigm

The law gives us the flexibility to calibrate our regulatory touch to the level of potential risk posed by new products



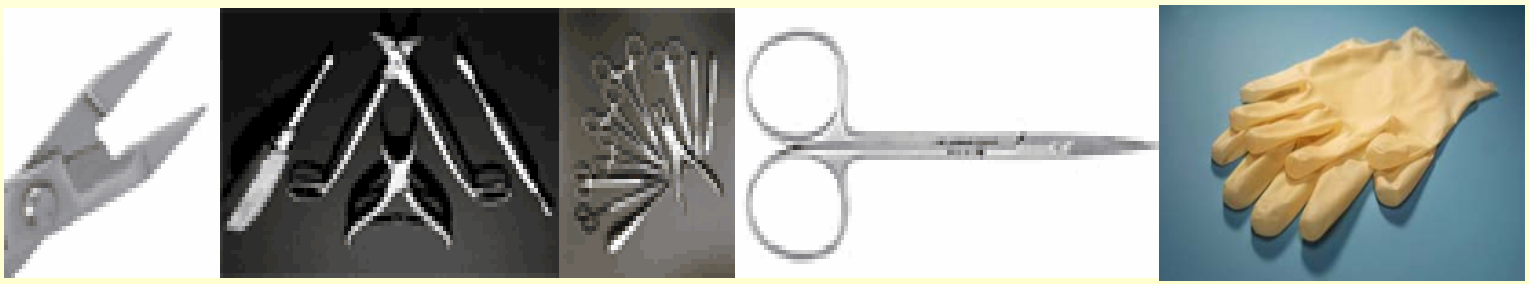
FDA's Approach – 5 Main Tenets

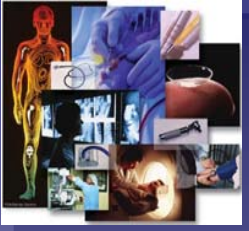
1. Base degree of control on risk
2. Weigh benefit vs. risk to determine safety and effectiveness
3. Use valid scientific evidence
4. Consider least burdensome means
5. Provide "reasonable assurance"



Risk-Based Paradigm
Class I

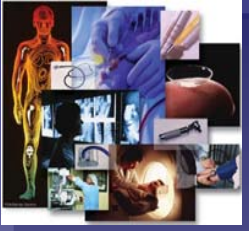
- **Simple, low risk devices**
- **General controls**
  - **E.g., registration, general recordkeeping requirements and compliance with Good Manufacturing Practice regulations (GMPs)**
- **Most exempt from premarket submission**





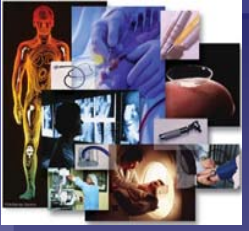
Risk-Based Paradigm
Class II

- **More complex, higher risk**
- **Subject to specific regulations or special controls**
  - E.g., meeting FDA-recognized performance standards, postmarket surveillance, patient registries
- **Premarket Notification [510(k)]**
  - Substantial equivalence
  - Performance testing
  - 10-15% require clinical data -Clinical trials usually confirmatory
    - Examples
    - Feasibility
    - Predicate controlled



Risk-Based Paradigm
Class III

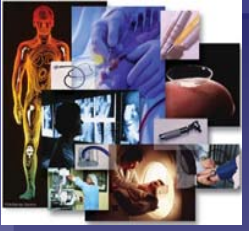
- **Most complex, highest risk**
- **Life-supporting, life-sustaining or important in preventing impairment of human health**
- **Premarket Application [PMA]**
  - Establish safety and effectiveness
  - Bench - Animal – Human Studies
- **May include post-approval study requirements**



Risk-Based Paradigm
De Novo & HDE

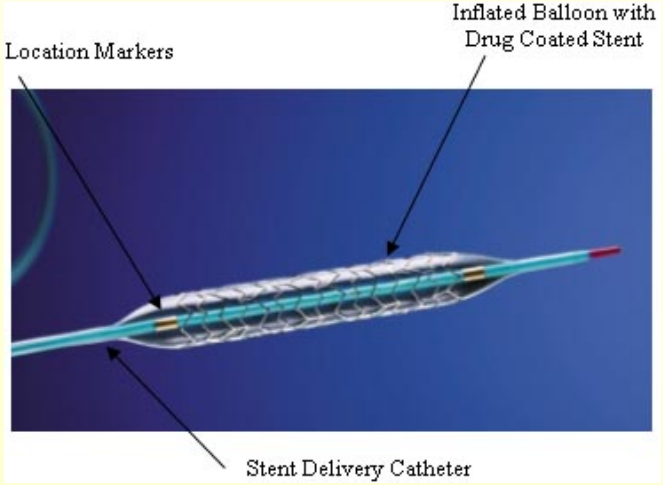
- **"De Novo"**
  - Device "types" that have never been marketed in the U.S., but whose safety profile and technology are now reasonably well understood

- **Humanitarian Device Exemption (HDE)**
  - Devices for orphan diseases
  - Intended to benefit patients in diagnosis and/or treatment of disease or condition affecting or manifested in fewer than 4,000 patients per year in the United States
  - Approval based on probable benefit

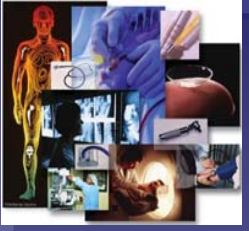


Combination Products

- **They are combinations of different types of medical products:**
  - Drug-device
  - Device-biologic
  - Drug-biologic
  - Drug-device-biologic

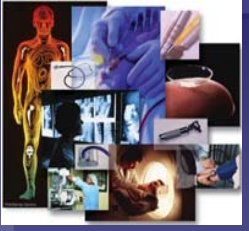


- **They can be:**
  - Physically or chemically combined
  - Co-packaged in a kit
  - Separate, cross-labeled products

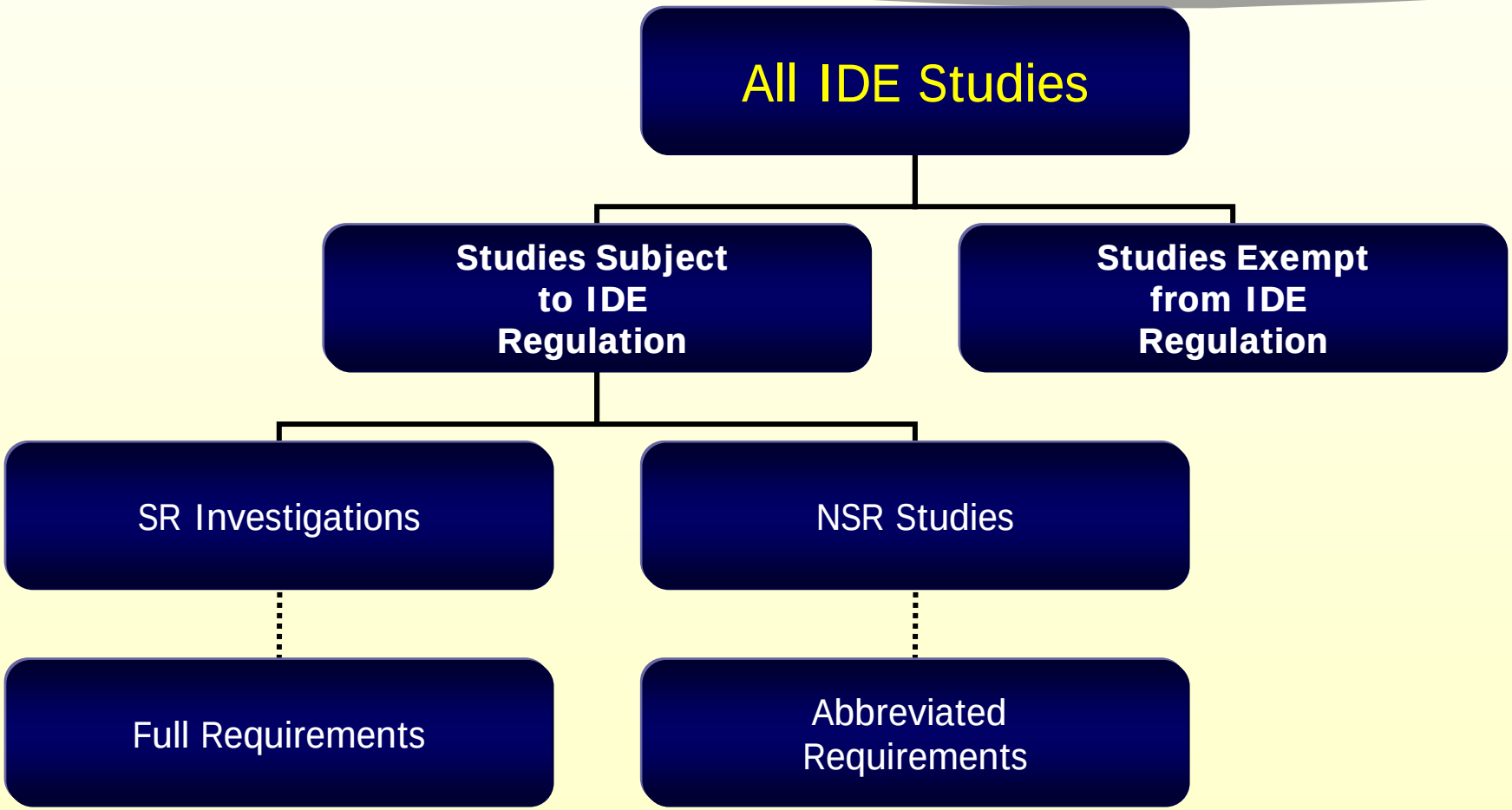


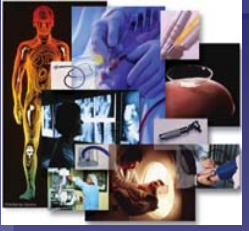
The Regulatory Pathway

1. **What is the proposed product? Device? Drug? Combination product?**
2. **What is the proposed *intended use?***
3. **What is the target population?**
4. **What are the risks? How are they mitigated?**
5. **What data are needed to demonstrate safety and effectiveness?**



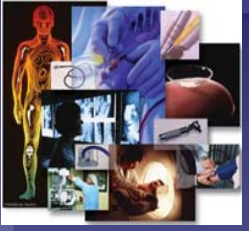
Investigational Devices





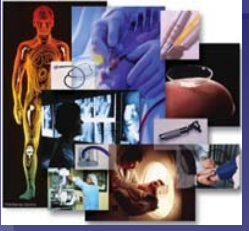
Clinical Trials

- **Feasibility – Phase I / II**
- **Pivotal – Phase III**
- **Postmarket – Conditions of Approval**



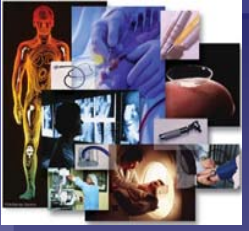
Feasibility (Phase I/II)

- 1 - 2 sites
- 5 - 10 subjects
- Initial safety data
- Modify device
- Modify treatment protocol
- No statistics



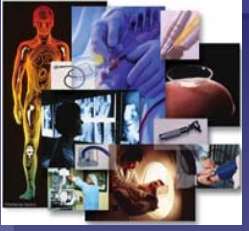
Phase II

- Confirm device design
- Confirm treatment protocol (instructions for use)
- Additional safety data
- Preliminary effectiveness data
- Estimate treatment effect for sample size calculation



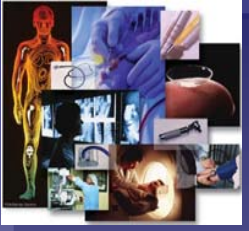
Pivotal (Phase III)

- Final design
- Final treatment protocol
- Clear hypothesis
- Controlled
- Valid statistical method
- Multisite



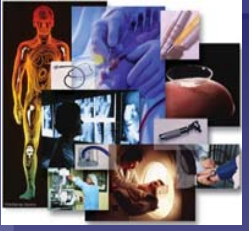
Condition of Approval Studies

- **Reasonable assurance of safety and effectiveness already established**
- **Answer specific questions not fully addressed in pivotal study**
  - Long-term results
  - Validation of surrogate
  - Panel concerns



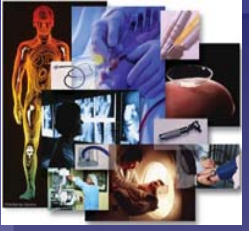
Guidance Development

- CDRH has instituted guidance prioritization
- CDRH more frequently reaches out to industry for drafts of guidance that would be useful
- CDRH added guidance development to its performance scorecard
- Guidance development is a question of resources; we need the right expertise to develop guidance and enough staff to work on guidance without sacrificing review performance



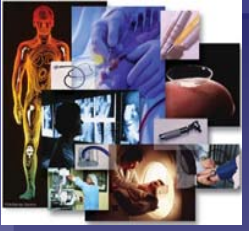
Guidance Development

- **Recently published guidance**
  - Analyte Specific Reagents (ASRs): FAQs
  - Handling Post-Approval Studies Imposed by PMA Order
  - In Vitro Diagnostic Multivariate Index Assays
  - Writing Dear Doctor Letters for Recalls of ICDs
  - Submissions for Medical Devices that Include Antimicrobial Agents
  - Statistical Guidance on Studies Evaluating Diagnostic Tests
  - PMA Supplement Decision-Making Process
  - Antimicrobial Susceptibility Test (AST) Systems
- **FY 2008 guidance agenda will be available on the CDRH website by mid-October**



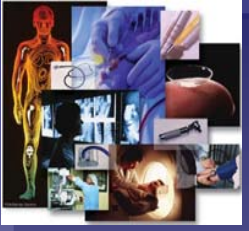
Standards Development

- **CDRH Standards Participation**
  - 38 Development Organizations
  - 238 Liaison Reps: 220 National Committees and 128 International Committees
  - 538 Standards Activities: 365 National and 173 Other Activities
- **A significant number of applications reference consensus standards**
  - CDRH recognizes over 700 national and international standards!



Quality System (QS) Regulations

- **Assure device safety and effectiveness through design and manufacturing controls**
- **Allow tailoring the controls based on to the type of device manufactured**
- **Are part of premarket review for Class III devices**
- **Are a key element of assuring postmarket safety for all devices**
- **Risk management techniques**
  - Are being formalized through standards and training programs
  - Are becoming more important to oversight of devices at all stages of the product lifecycle
- **Harmonization**
  - FDA is involved in harmonization through GHTF
  - Quality systems programs for devices in regulations and standards globally are currently quite consistent with FDA QSR

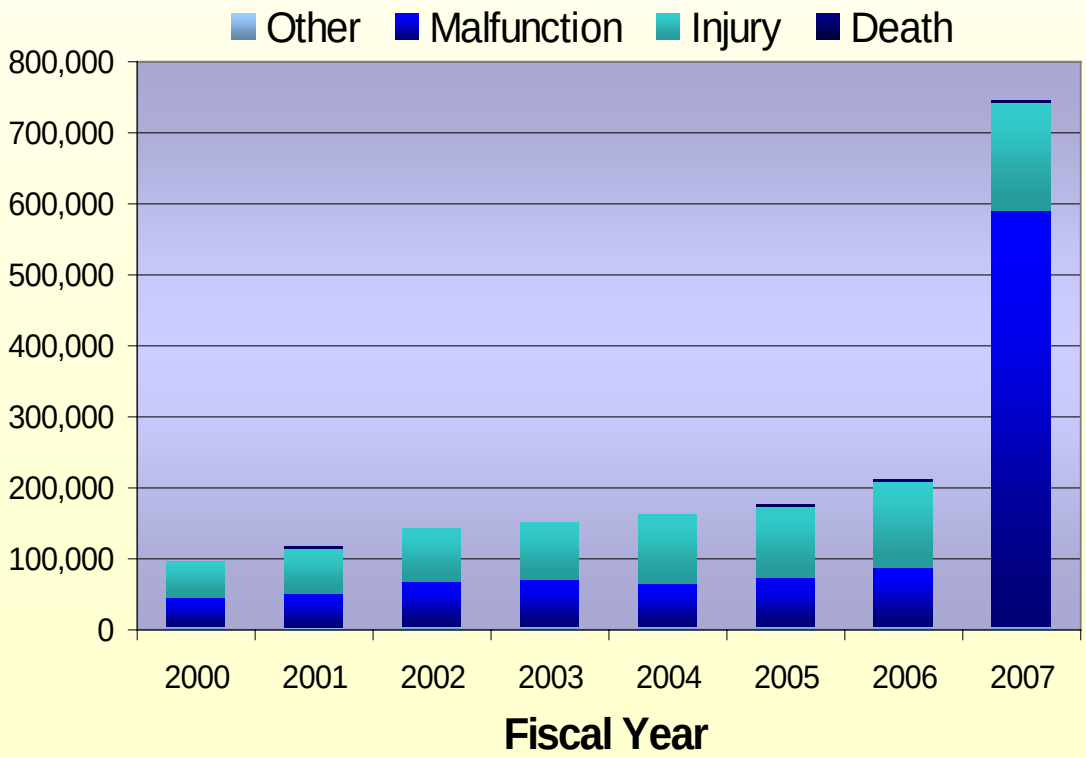


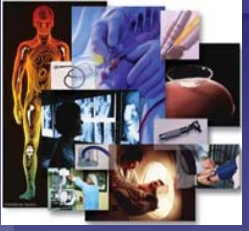
MDR

- **eMDR**
- **Now available for electronic submission of medical device adverse event reports**

How to submit:

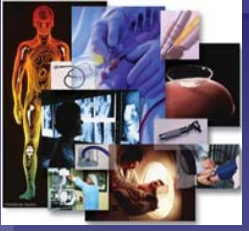
- **Please Contact CDRH before using eMDR Indira.Konduri@fda.hhs.gov**
  - Small volume** (one report at a time) - through eSubmitter
  - Large volume** (batch) - Contact CDRH





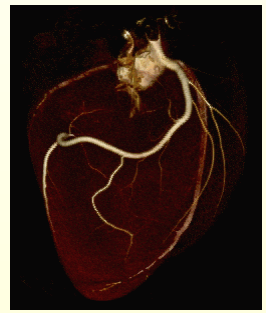
MedSun

- **Targeted Surveillance**
- **New tools:**
  - LabNet
  - HeartNet
  - TissueNet (with CBER)
  - KidNet
- **New work items for FY08:**
  - HomeNet
  - AudioNet
  - EyeNet

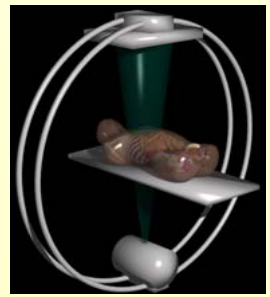


Research Prioritization

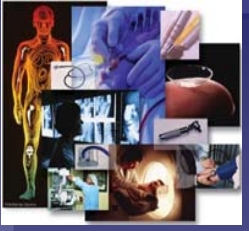
- **Peer review type process to evaluate research activities**
- **Involves internal and external scientific experts and internal regulatory experts from the premarket, postmarket, and compliance components of the Center**
- **Review process takes into account science and relevance**
- **Have:**
  - Resulted in a more focused and productive research enterprise
  - Forged collaborations across the Center and outside the Center



Cone-beam CT



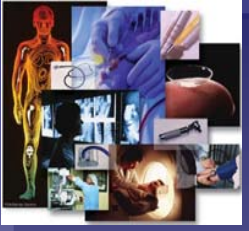
Virtual Cath Lab



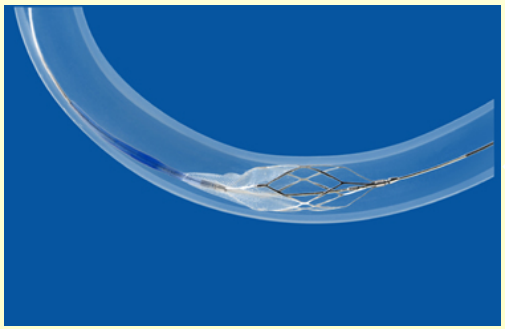
Nanotechnology

What are we doing?

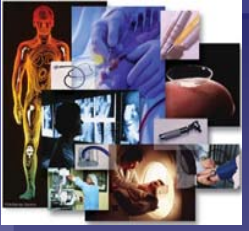
- Working on a mechanistic understanding of physical, chemical and biological processes
- Determining applicability of existing test methods and standards
- CDRH projects include
  - Stability of Nano-scale Constructs
  - Blood Damage in Medical Devices
  - Critical Properties and Biological Effects of Nanoparticles



Biomaterials

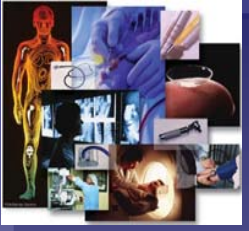


- **Objective, standardized preclinical testing methods**
  - Material properties
  - Biocompatibility
- **Appropriate use of standards and guidances**
  - www.fda.gov/cdrh
- **Combination products issues**
  - Multiple Centers
  - Regulations
- **Biomaterials testing must change as biomaterials change**
  - Animal studies when using biomaterials such as protein products (e.g., growth factors),



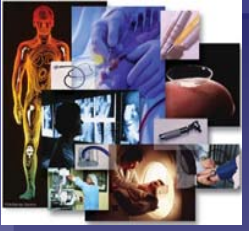
Communication of Risk/benefit Information

- **Medical Device in Emergency Situations**
  http://www.fda.gov/cdrh/emergency/index.html
- **Medical Device Recalls - The redesigned website provides a web-friendly, plain language overview of medical device recalls**
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfTopic/medicaldevicesafety/recalls.cfm
- **Hospital Bed Safety**
  http://www.fda.gov/cdrh/beds/index.html
- **Phakic Intraocular Lenses**
  http://www.fda.gov/cdrh/phakic/
- **Maturity Health Matters**
  www.fda.gov/cdrh/maturityhealthmatters/
- **E-Consumer Initiative – New services available include email suscription management system and Real Simple Syndication (RSS) feeds**



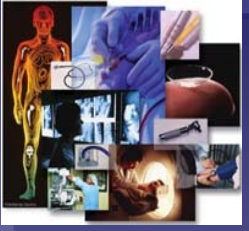
CDRH FY 2008 Priorities

1. Continue implementation of the postmarket transformation initiative
2. Implement MDUFMA II
3. Continue implementation of IT solutions and collaborate with agency in the development of enterprise solutions
4. Optimize the potential of each individual to help meet the needs of the Center today and tomorrow
5. Enhance device development through focused research and increased collaboration
6. Build on successful transition to White Oak



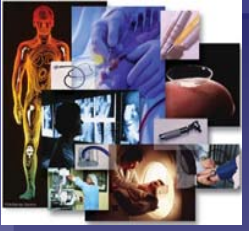
MDUFMA II/FDAAA

Benefits to Public Health	MDUFMA II Goal
Patients and practitioners will have access to safe and effective medical devices more quickly	Continued improvement in device review times and greater transparency of the review process
FDA will have the resources to maintain the cutting edge scientific expertise necessary to provide timely review and ensure the safety of the increasingly complex devices of tomorrow	Adequate and stable funding for FDA
FDA can better focus its inspectional resources on higher risk devices	Enhance the third party inspection program



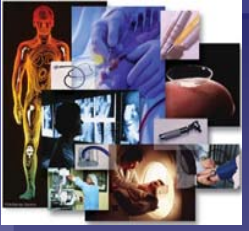
MDUFMA II/FDAAA Performance Goals

- **Quantitative Goals**
  - Proposing continued improvements with current staffing levels
  - Goals
    - **Eliminate the cycle goals**
    - **Two-tiered decision goals**
    - **New goals for some application types**
- **Qualitative Goals**
  - Interactive review
  - Maintenance of performance
  - Guidance document development
  - Quarterly updates
  - Meetings
  - Reviewer training
  - Imaging devices
  - IVDs



Comparison of Quantitative Decision Goals in MDUFMA I and II

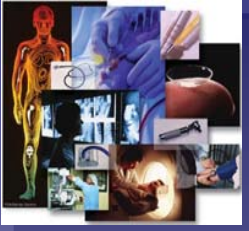
MDUFMA I	MDUFMA II
PMA Final Decision Goals	
50% of PMAs and panel track PMA supplements in 180 days	60% of PMAs and panel track PMA supplements in 180 days
90% of PMAs, panel-track supplements, premarket reports in 320 days	90% of PMAs and panel track PMA supplements in 295 days
NA	50% of expedited PMAs and expedited panel track PMA supplements in 180 days
90% of expedited PMAs in 300 days	90% of expedited PMAs and expedited panel track PMA supplements in 280 days
Modular PMA Goals	
NA	75% of PMA modules in 90 days
NA	90% of PMA modules in 120 days
510 (k) Goals	
80% of 510(k)s in 90 days	90% of 510(k)s in 90 days
NA	98% of 510(k)s in 150 days



MDUFMA II/FDAAA

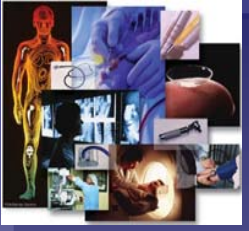
Third Party Program Recommendations

- **Streamline administrative burdens**
  - Firms would provide FDA 30 day notice of their intent to use an AP rather than petitioning FDA for clearance to use an AP
- **Expand participation**
  - Firms may use an AP for an unlimited number of consecutive inspections without seeking a waiver, rather than only two consecutive inspections
  - FDA would continue to conduct “for cause” or follow-up inspections at our discretion
- **Encourage industry to provide FDA with more data**
  - Firms may voluntarily submit reports by third parties assessing conformance with appropriate international quality systems standards, such as ISO, which FDA would consider in setting our inspectional priorities



Unique Device Identifier (UDI) System for Medical Devices

- **A unique device identifier system could have broad applications in:**
  - Reducing medical errors
  - Facilitating device recalls
  - Improving medical device adverse event reporting
  - Encouraging cost effectiveness by improving delivery and supply chain efficiency
- **Public meeting held on October 25, 2006**
- **Public Docket - Evaluating comments**
- **FDA Amendments Act of 2007 –**
  - Establish a unique identification system
  - **www.fda.gov/cdrh/ocd/udi/**



Thank you!

www.fda.gov/CDRH