Medical Device Regulation

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Development and Approval of Drugs and Devices
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Educational Objectives

Learn

- how to determine if a product is a medical device
- medical device's risk-based classification
- the differences in the requirements to register different device classes
- how to register changes in existing devices

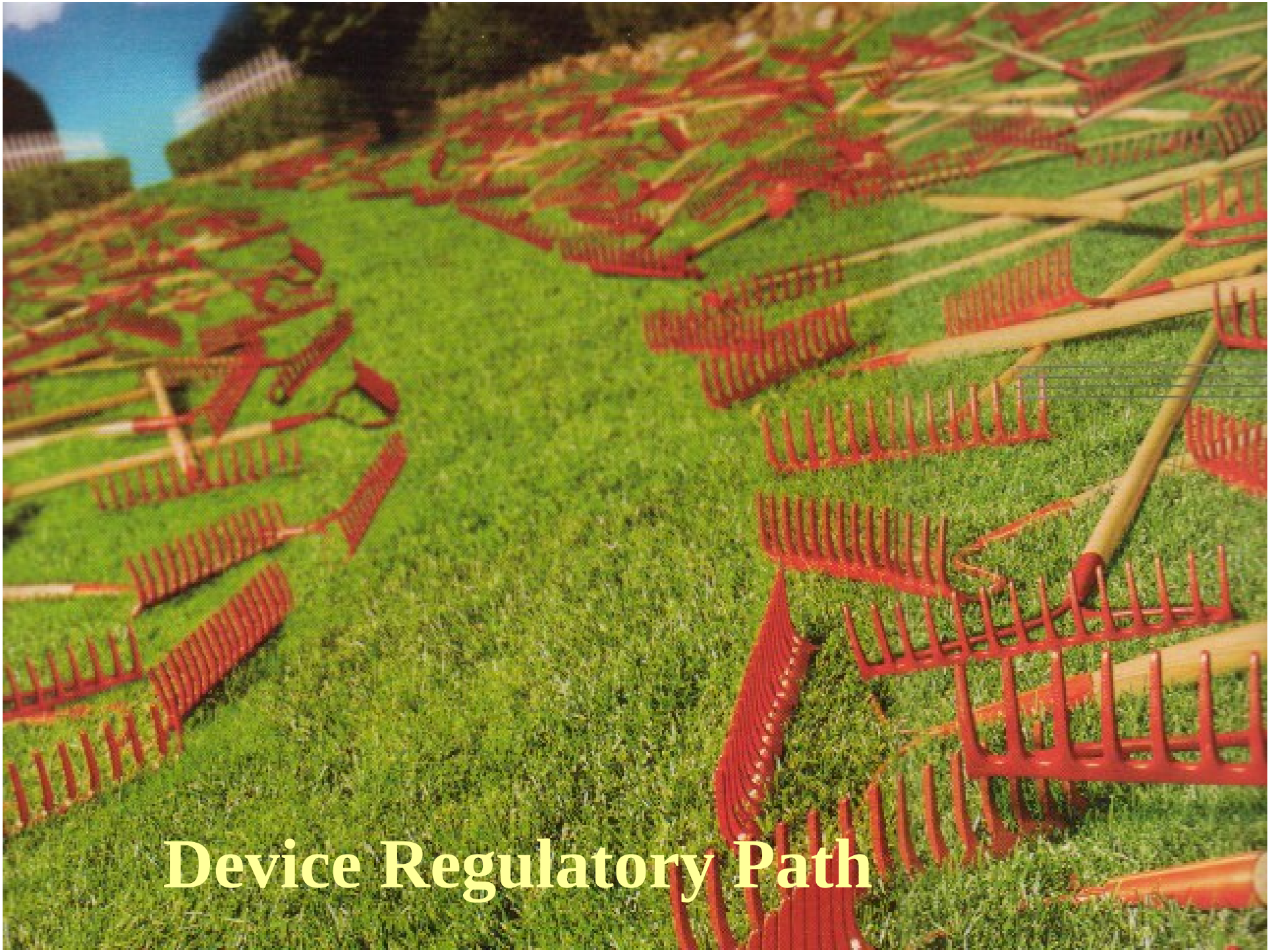
Safe Therapeutic Products

Drugs

- Pure molecules
- Toxicology
- Short half-life
- Long market life
- Drug interactions
- Wrong Drug / Dose
- Clinically studied
- Good Manufacturing Practices (cGMP)

Devices

- Complex components
- Biocompatibility
- Durable Equipment
- Rapid product cycles
- Malfunction
- User Error
- Bench studied
- Quality Systems (ISO 13485)


Device Regulatory Path

Drug vs. Device: Translation of Terms

- Investigational New Drug exemption (IND)
- New Drug Application (NDA)
- abbreviated New Drug Application (aNDA) 505(j) and 505(b)(2)
- Orphan Drug
- FDA Monographs / USP / NCLS standards
- Advisory Committee

- Investigational Device Exemption (IDE)
- Pre-Market Authorization (PMA)
- 510(k)
  - Based on predicate device
  - De Novo (without predicate)
- Humanitarian Device Exemption (HDE)
- Recognized Standards (ISO, AMII, ASTM, NCLS …)
- Advisory Panel

Drug vs. Device: Translation of Terms

- International Conference on Harmonization of technical standards (ICH)
- Adverse Drug Report (ADR)
- Adverse event reporting system (AERS)
- Prescription Drug User Fee Act (PDUFA) 1992
- Special Protocol Assessment
- Global Harmonization Taskforce (GHTF)
- Medical Device Report (MDR)
- Manufacture and user facility device experience (MAUDE)
- Medical Device User Fee and Modernization Act (MDUFMA) 2004
- Agreement and Determination Meetings

Is a product a Medical Device?

Legal Definitions:

- Food Drug and Cosmetic Act
  - Drugs vs. Medical Devices
  - Combination Products
- Public Health Service Act
  - Biologics

FDA Regulations

- Device Classifications

FDA practices and precedents

Definition of a Drug

The term "drug" means:

… articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals;

… articles (other than food) intended to affect the structure or any function of the body of man or other animals.

Definition of a Devices

Instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is -

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and …

Definition of a Devices

… and,

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

Classification Heirarchy

Devices are:

- Drugs

  … which do not act by chemical or metabolic means

  …

Or:

- Instrument, apparatus, …

Is this a medical device ?

Treadmill Regulation

Title 21--Food and Drugs Chapter I – FDA, HHS
Subchapter H – Medical Devices

PART 890 -- PHYSICAL MEDICINE DEVICES

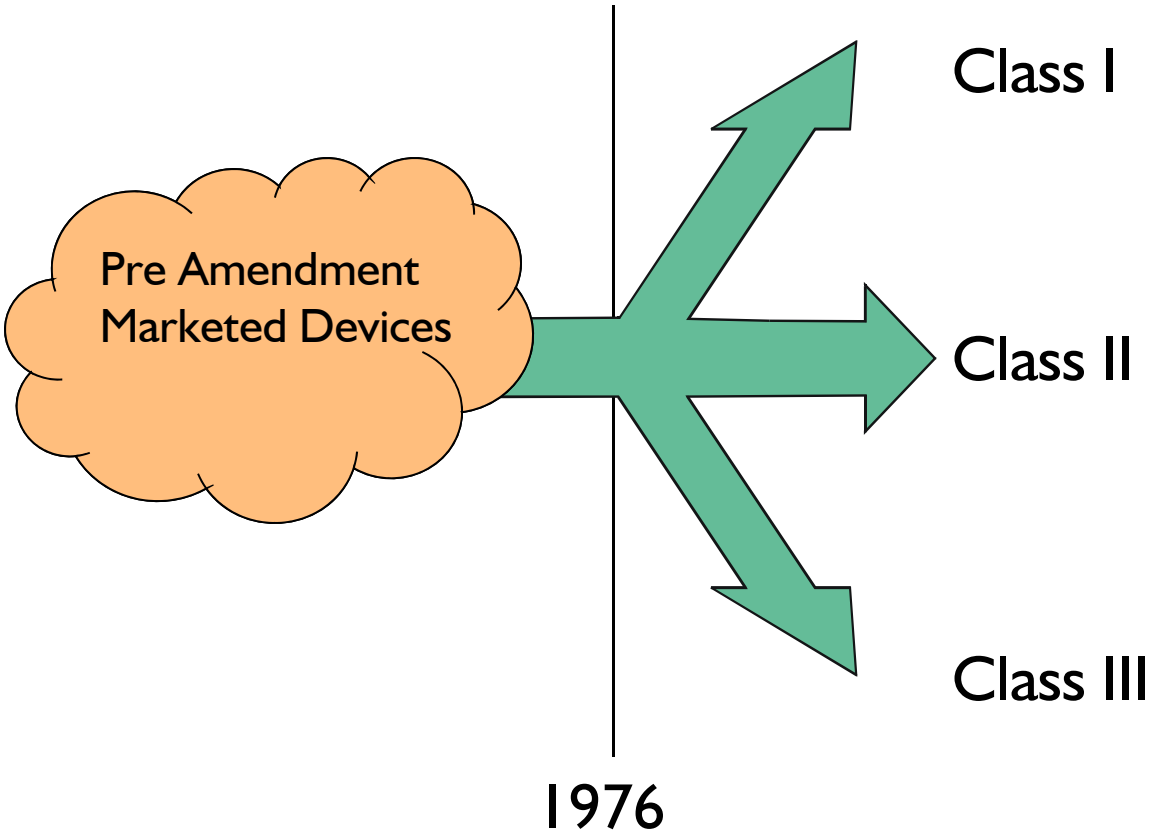
Subpart F--Physical Medicine Therapeutic Devices Sec.

890.5380 Powered exercise equipment.

(a) Identification. Powered exercise equipment consist of powered devices *intended for medical purposes*, such as to redevelop muscles or restore motion to joints or for use as an adjunct treatment for obesity. Examples include a powered treadmill, a powered bicycle, and powered parallel bars.

(b) Classification. Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter, subject to the limitations in 890.9.

Device Regulatory Path



1976: Device amendments to FD&C Act

Three classes of devices:

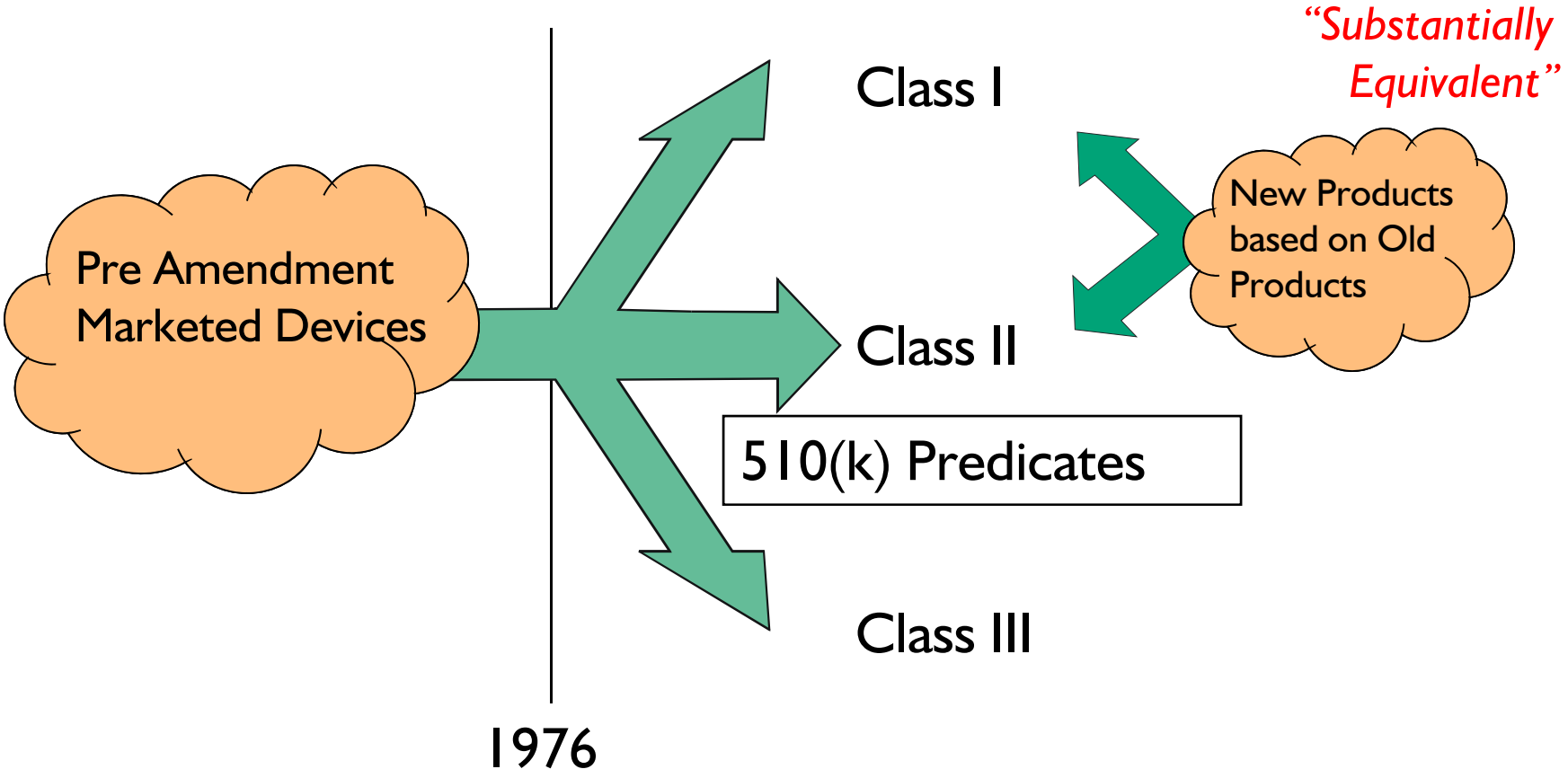
- Class I:
  - Pose least risk to patient, Not life sustaining
  - GMP, proper record keeping required
  - 30% of devices
  - X-ray film, tongue depressors, stethoscopes
- Class II:
  - Not life sustaining, but must meet performance standards
  - Blood pressure monitors, Catheter guide wires
  - > 60% of devices

1976: Device amendments to FD&C Act

Three classes of devices:

- Class III:
  - Pose greatest risk to patient
  - For use in supporting or sustaining human life
  - < 10% of devices
  - Stents, heart valves, LVADs
  - Require GMP, animal tests, human clinical studies under IDE

Device Regulatory Path



510(k)

- Substantially Equivalent – New device is compared to a similar device that is on the market.
- Device need be only as good (or bad) as what was on market in 1976 – but can be better
- 510(k) clearance does not assure effectiveness
- Many devices are exempt from 510(k) submission (all Class 1, some Class 2)
- Review time about 90 days

Substantial equivalence

- Same intended use as predicate device
- Same technological characteristics as predicate device
- *Or* … different technological characteristics that do NOT raise new questions of safety or efficacy

Case Study: Immunicon

IMMUNICON®
Cellular Information for Better Healthcare

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HOME | PRODUCTS | TECHNOLOGY | ABOUT IMMUNICON | INVESTOR INFO

Your Path: Home > Products > Overview

- Products Overview
- CellTracks® AutoPrep® System
- CellTracks® Analyzer II
- Kits and Marker Reagents
- CellSave® Preservative Tube
- Pharma Services
- Order Information

Overview of Products and Services

Immunicon has developed a portfolio of products to capture, count and character
CellSave® Preservative Tube is for the collection and preservation of whole bloo
CellTracks® AutoPrep® System is used with our reagent kits to automate and st
isolation of circulating tumor cells or circulating endothelial cells. Cellular analysis
performed using the CellTracks® Analyzer II or samples may be processed off-li
molecular analysis.

Pharma Services

Immunicon collaborates with pharmaceutical and biotechnology companies on as
and we offer clinical trial testing services to incorporate rare cell analysis into dru
programs. READ MORE

Products for Rare Cell Analysis

The CellSave® Preservative Tube is for the collection and preservation of circulating epithelial cells (tumor cells) to be used for enumeration and phenotyping.

>>READ MORE<<

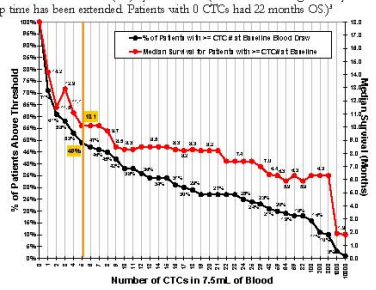
Kits and Marker Reagents are available for isolation and analysis of circulating tumor cells (CTCs) and circulating endothelial cells (CECs).

>>READ MORE<<

Prevalence of CTCs at Baseline

CTC vs. Survival for 177 Metastatic Breast Cancer Patients

The chart shows overall survival (OS) by CTC count. (Note: Since the original analysis was performed, follow-up time has been extended. Patients with 0 CTCs had 22 months OS.)[2]

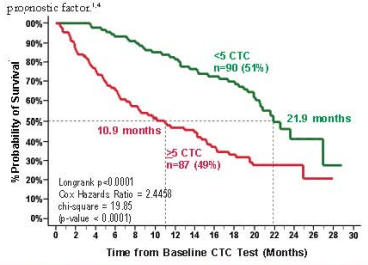


- The X-axis shows the number of CTCs per 7.5 ml of whole blood.
- The orange vertical line indicates the threshold of ≥5 CTCs selected as the diagnostic cutoff.
- The left Y-axis and **black line** show the percentage of patients above the CTC threshold.
- The right Y-axis and the **red line** show the median survival in months. For example, 49% of the patients had ≥5 CTCs and median survival of 10.1 months, whereas 71% of patients had 1 or more CTCs and 14.2 months median survival.

Survival Analysis using ≥5 CTC Threshhold

Overall Survival Analysis Using Baseline CTC Values

- Patients with 5 or more CTCs at baseline had worse overall survival (OS) compared to patients with less than 5 CTCs. The median OS was 10.9 months for CTC positive patients compared with 21.9 months for CTC negative patients.[3]
- In multivariate analyses that included clinical and pathological factors, CTCs were the strongest prognostic factor.[1,4]



Case Study: Immunicon

Regulatory Approvals

- All 510(k) approvals
- Separate approvals for different system components

IMMUNICON CELLTRACKS ANALYZER IMMUNICON CORP. K030263 GKZ ... more

IMMUNICON CELLSAVE PRESERVATIVE TUBE IMMUNICON CORP. K030596 JKA ... more

IMMUNICON CELLTRACKS AUTOPREP SYSTEM IMMUNICON CORP. K040077 GKH ... more

CELLTRACKS ANALYZER II IMMUNICON CORP. K060110 NQI ... more

CELLTRACKA ANALYZER II IMMUNICON CORP. K050145 NQI ... more

CELLPREP SAMPLE PREPARATION SYSTEM, MODEL 9518 IMMUNICON CORP. K022512 GKH ... more

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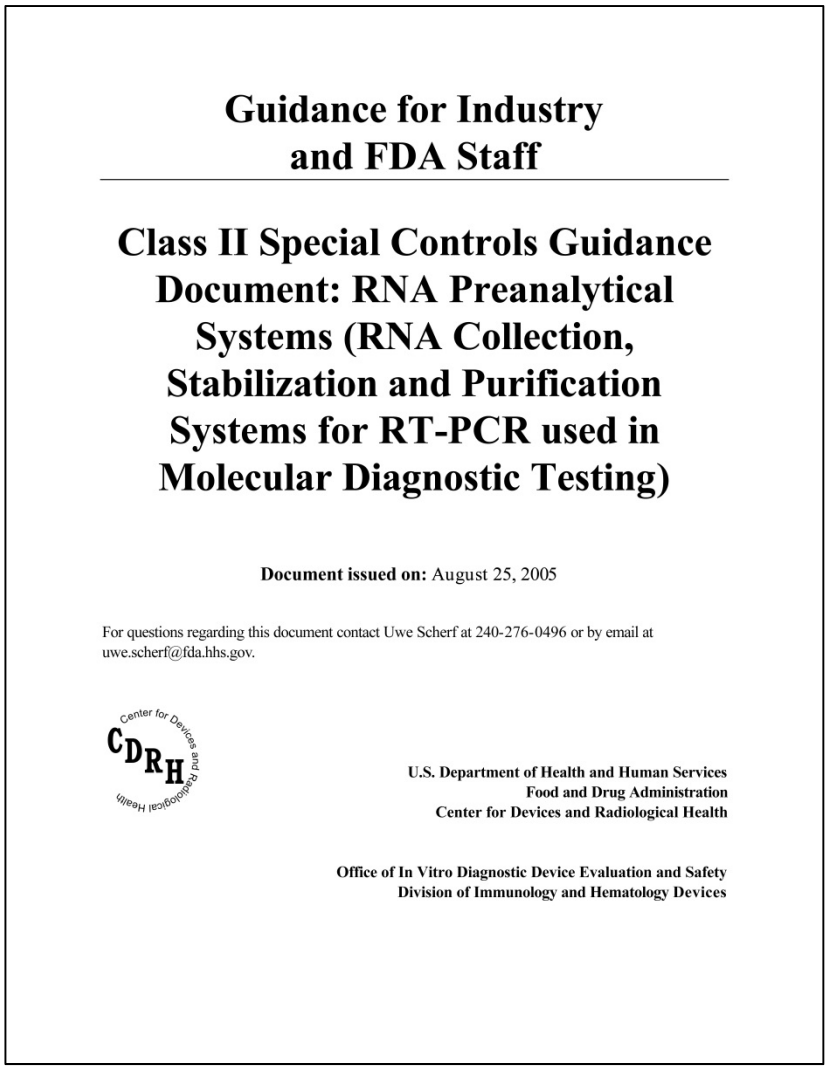
FDA Guidance: RNA Collection



Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: RNA Preanalytical Systems (RNA Collection, Stabilization and Purification Systems for RT-PCR used in Molecular Diagnostic Testing)

Document issued on: August 25, 2005

For questions regarding this document contact Uwe Scherf at 240-276-0496 or by email at uwe.scherf@fda.hhs.gov.

Center for Devices and Radiological Health
CDRH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Immunology and Hematology Devices

13 Page Document

Class II
RNA Preanalytical Systems

- The device may consist of
  - sample collection devices,
  - nucleic acid isolation and purification reagents, and
  - processing reagents/equipment (tubes, columns, etc.).
- It also may contain
  - instruments for automation of the nucleic acid isolation and purification steps.

Types of 510(k) submissions

Traditional

- Must include all required information and data

Special

- For modifications to a device already under 510(k)
- Excludes modifications to intended use or fundamental scientific technology

Abbreviated

- Certify that you have followed FDA guidance documents, special control, and/or recognized consensus standards

Who must submit 510(k)

- Domestic manufacturers introducing a device into the market
- Specification developers introducing a device into the market
- Repackers or relabelers who make labeling changes or whose operation significantly affects the device
- Foreign manufactures/exporter or US importer introducing a device into the US market

When a 510(k) is required

- When introducing a device into the market for the first time
- New intended use for a device already in distribution
- Change or modification to a device already on the market, if it can significantly affect safety or effectiveness

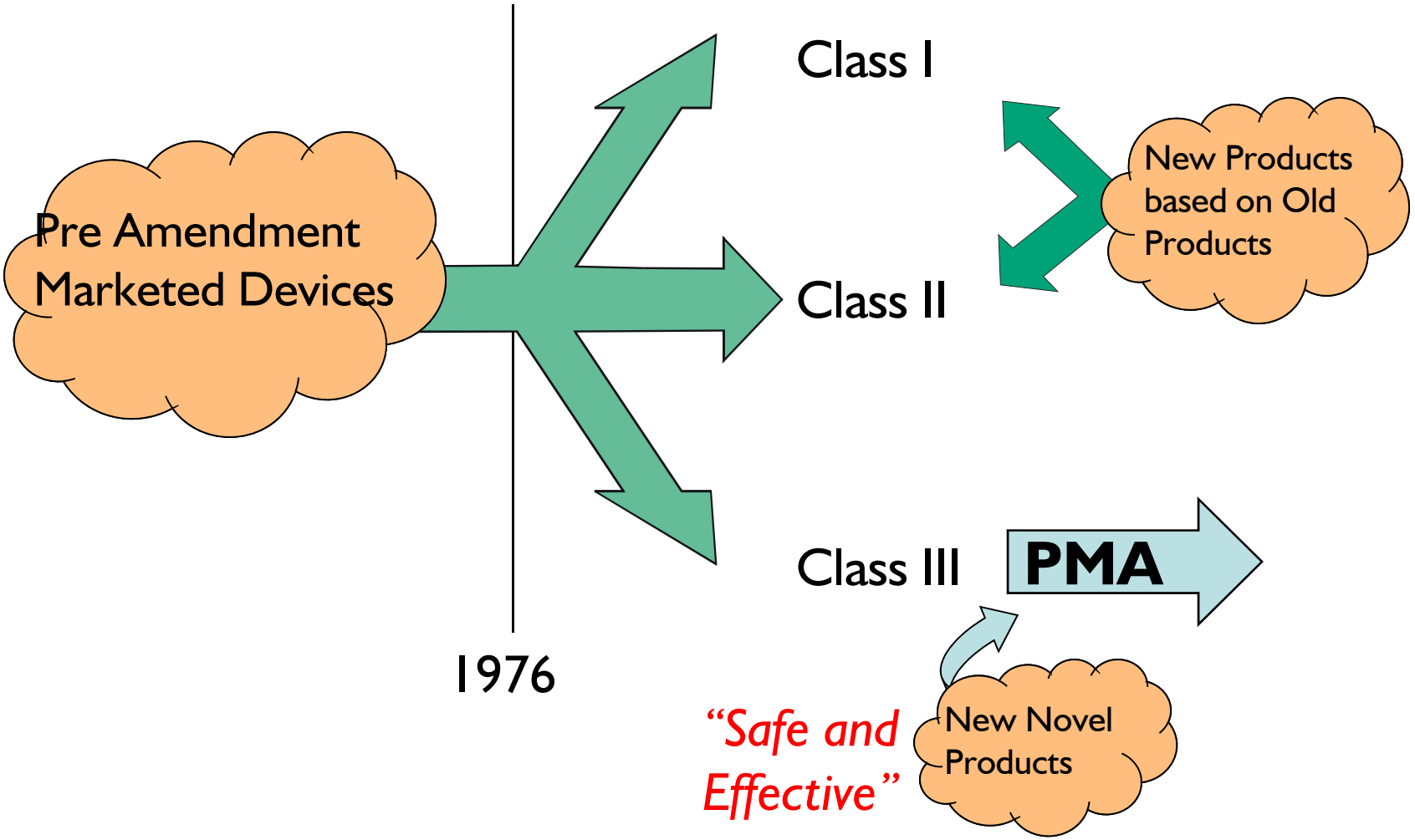
Advantages of a 510(k) over PMA

Even when a 510(k) requires clinical trials … *

- 510(k) applications are very streamlined
- They are approved on average in 90 days vs. 400 days
- There are no annual or periodic reports
- There are no product supplements
- Labeling changes may be done without prior approval
- Manufacturing changes may be done without prior approval

* And 90% do not

Device Regulatory Path



PMA

- Devices that sustain life, implants, in class III, or can not be shown substantially equivalent are approved by PMA process

- In a PMA the sponsor must demonstrate that the device is safe and effective for intended use

PMA Content

- Indications for use
- Device description
- Laboratory testing
- Preclinical studies
- Results of Clinical studies
- Labeling
- Manufacturing (GMP) information
- Summary of Safety and Effectiveness

PMA Review Process

- Multi discipline review
- May be reviewed by FDA advisory panel
- FDA review time = 180 days
- Data is proprietary

PMA Approval Process

Device + intended use considered together

Manufacturer submits request for marketing approval

Advisory panel:

- One consumer representative (non-voting)
- One industry representative (non-voting)
- Physicians and scientists

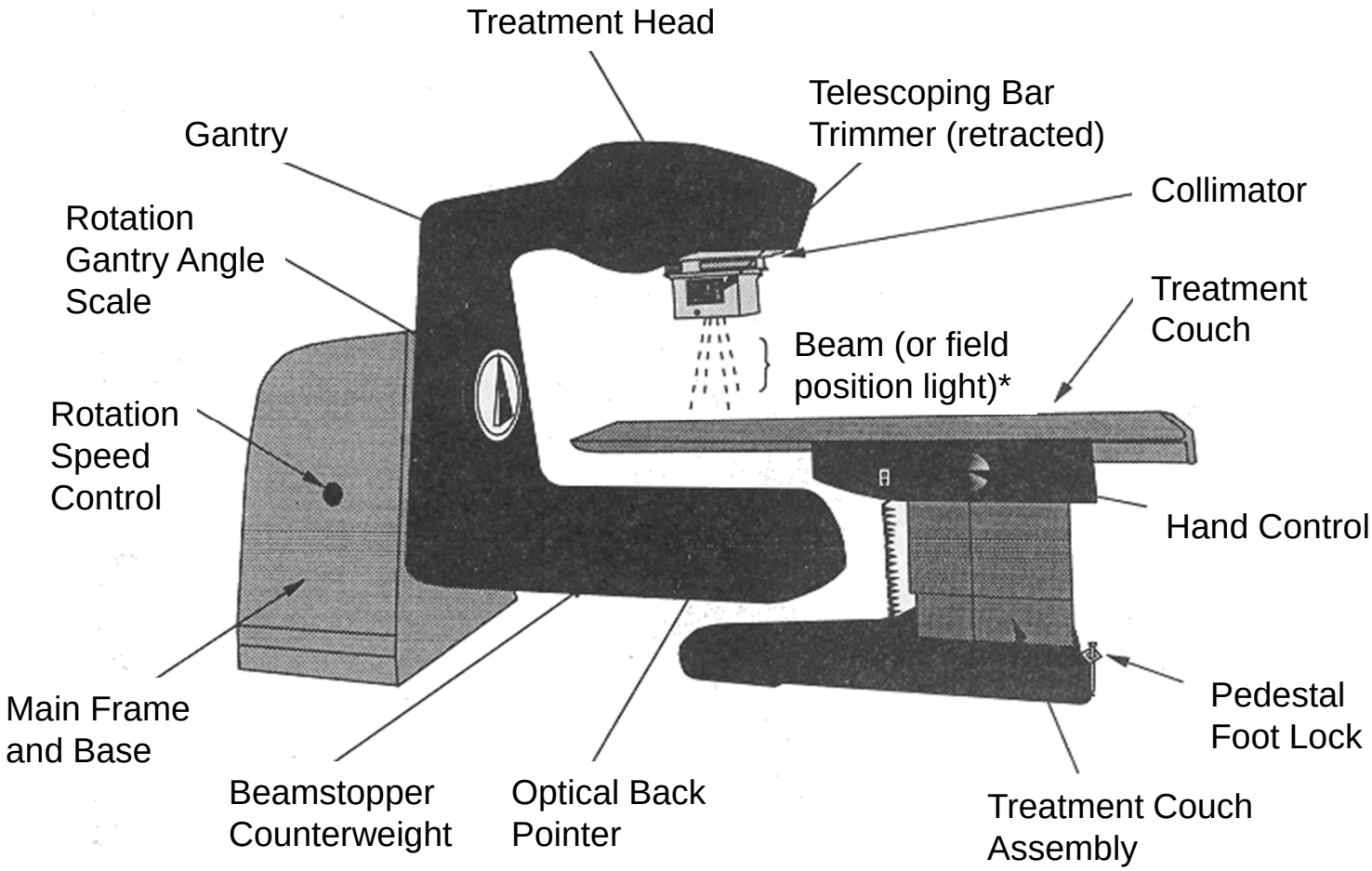
FDA not required to follow recommendations of panel, although they usually do

Details, details

- PMA *applications* are *approved* when they are found to be *safe and effective*
- 510(k) *notifications* are *cleared* when they are found to be *substantially equivalent*
- Exempt devices are *registered* and *listed* (like all medical devices)

Class 3 (PMA) or Class 2 (510(k)) ?

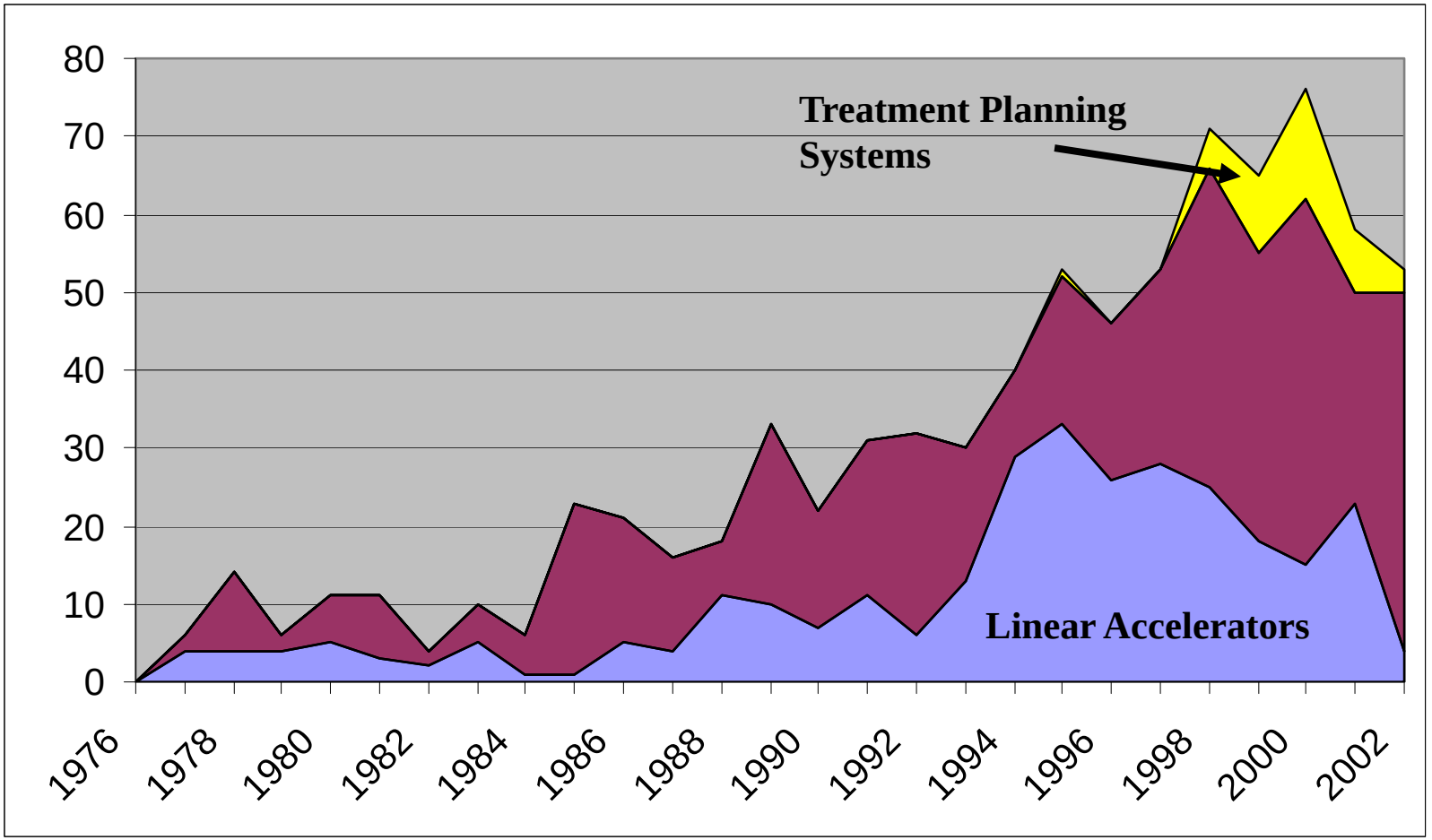
Overall configuration of radiation treatment machine



Radiation Therapy Device Categories

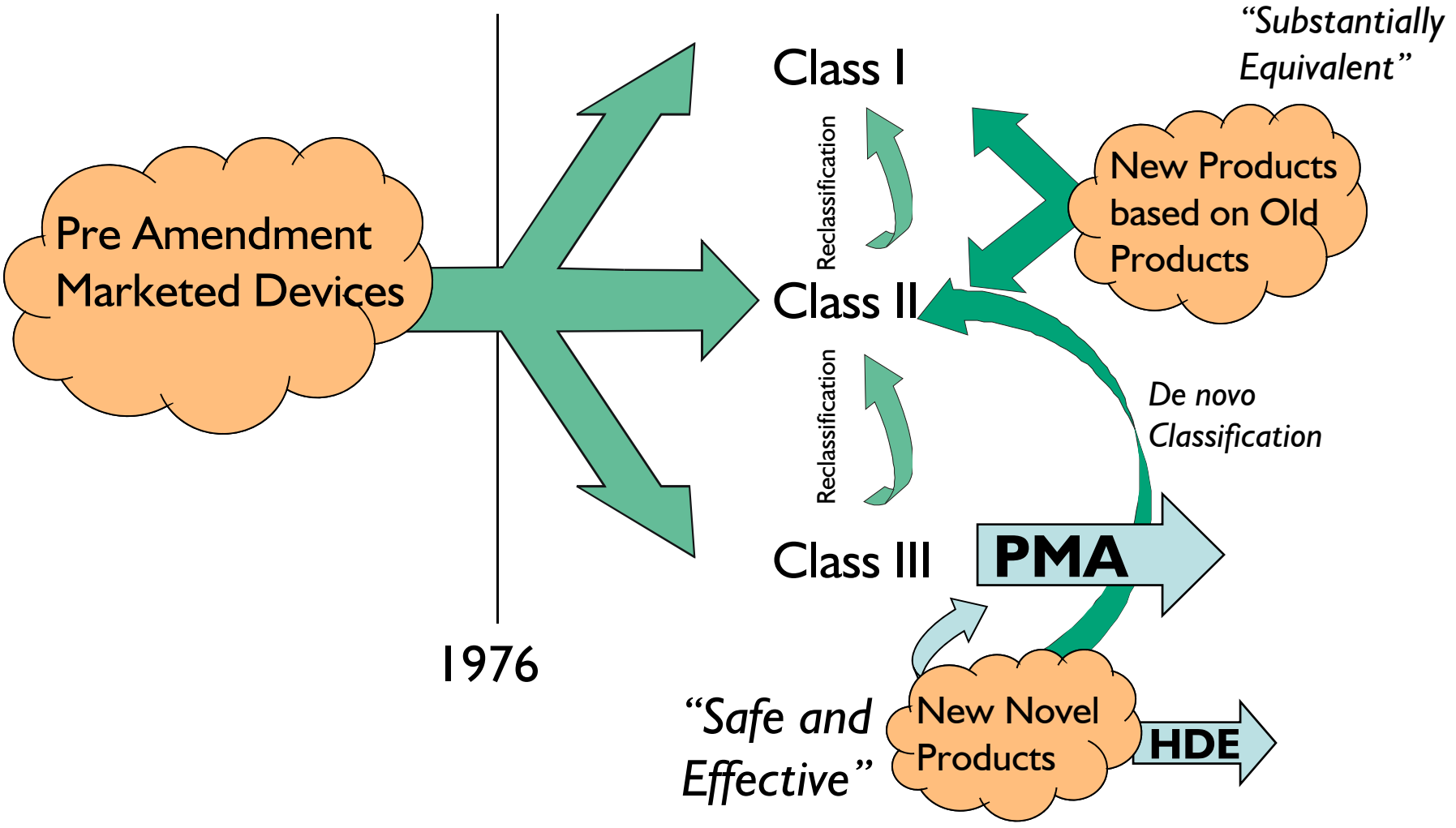
- Linear accelerator
- System, radiation therapy,
  - charged-particle, medical
  - neutron, medical
  - Radionuclide
  - therapeutic, x-ray
- Synchrotron, medical
- Block, beam-shaping, radiation therapy
- Generator,
  - dermatological (grenz ray), therapeutic x-ray
  - high voltage, x-ray, therapeutic
  - low voltage, therapeutic x-ray
- Collimator,
  - dermatological, therapeutic x-ray
  - orthovoltage, therapeutic x-ray
- Device, beam limiting,
  - teletherapy, radionuclide
  - x-ray, therapeutic
- Couch, radiation therapy, powered
- Monitor, patient position, light-beam
- Seed, isotope, gold, titanium, platinum
- Source,
  - brachytherapy, radionuclide
  - isotope, sealed, gold, titanium, platinum
  - wire, iridium, radioactive
- System, applicator, radionuclide,
  - manual
  - remote-controlled
- Radiation Therapy Simulation System
- Radiation Therapy Planning System

Radiation Therapy Product Approvals by Year



510(k) Approvals

Device Regulatory Path



Humanitarian Device Exemption

HDE

- Device designed to treat or diagnose condition that affects <4,000 patients/year
- Device would not otherwise be available without exemption
- No comparable device is available
- Patients will not be exposed to unreasonable or significant risk of injury or illness by device

Humanitarian Device Exemption

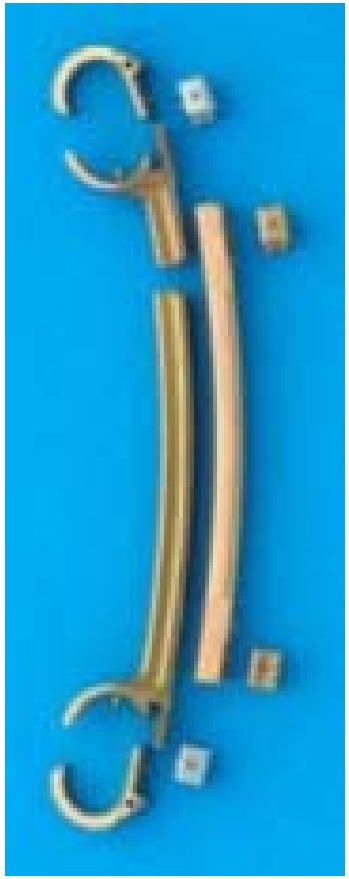
- Manufacturers seeking premarket approval for new medical devices ordinarily must show that products are safe and effective.

- To encourage development of medical devices for rare diseases, FDA will approve such devices if manufacturers demonstrate the safety and probable benefit to patients.

Case Study, HDE

Vertical Expandable Prosthetic Titanium Rib

- Indication
  - Treatment of thoracic insufficiency in children
- Biocompatibility and mechanical testing
- Clinical trials: 247 patients with 5 years of follow-up in single-armed trials assessing growth and pulmonary function



HDE vs. PMA

- Both are marketing approvals
- Approval thresholds differ:
  - PMA – safety and effectiveness
  - HDE – safety and probable benefit
- IRB approval required for HDE
- Profit not allowed for HDE (can recover costs of R&D, manufacturing and handling)

Drugs and Devices used Together

Diagnostics
- Drug levels
- Biomarkers

Imaging
- Disease Response
- Pharmacodynamics

Outcome measuring devices
- Treadmill / spirometry
- Body composition

Software

Drugs as Accessories to Devices
- Antibiotic bone cement
- Contact lens solutions
- Heparin flushes

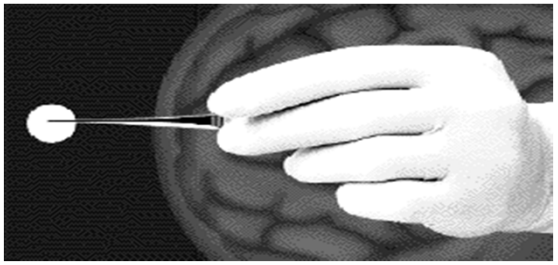
Drug Delivery Devices
- Aerosol / Gas
- Pumps
- "Containers"
  - Liposomes, Nanoparticles
- Patches
- Prefilled syringes
- Drug releasing implants

Drugs which are Devices
- Injected hyaluronic acid
- "Street side" dialysis solutions

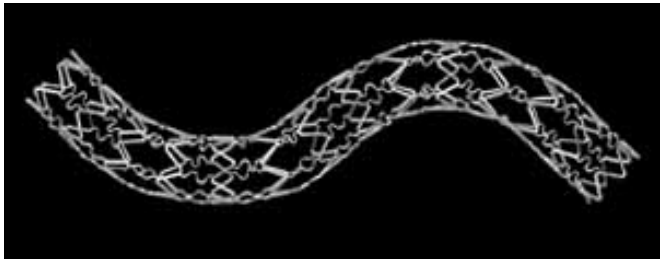
Combination Products
- Titanium cage + BMP

Combination Products

Drug Eluting Disk



Drug Eluting Stent



Combination Product

Combination Product 21§3.2(e)

- Two or more products:
  - … combined or mixed as a single entity
  - … packaged together
  - … packaged separately but … where both are required

Not:

- Drug-Drugs*
- Device-Devices
- Biologic - Biologic

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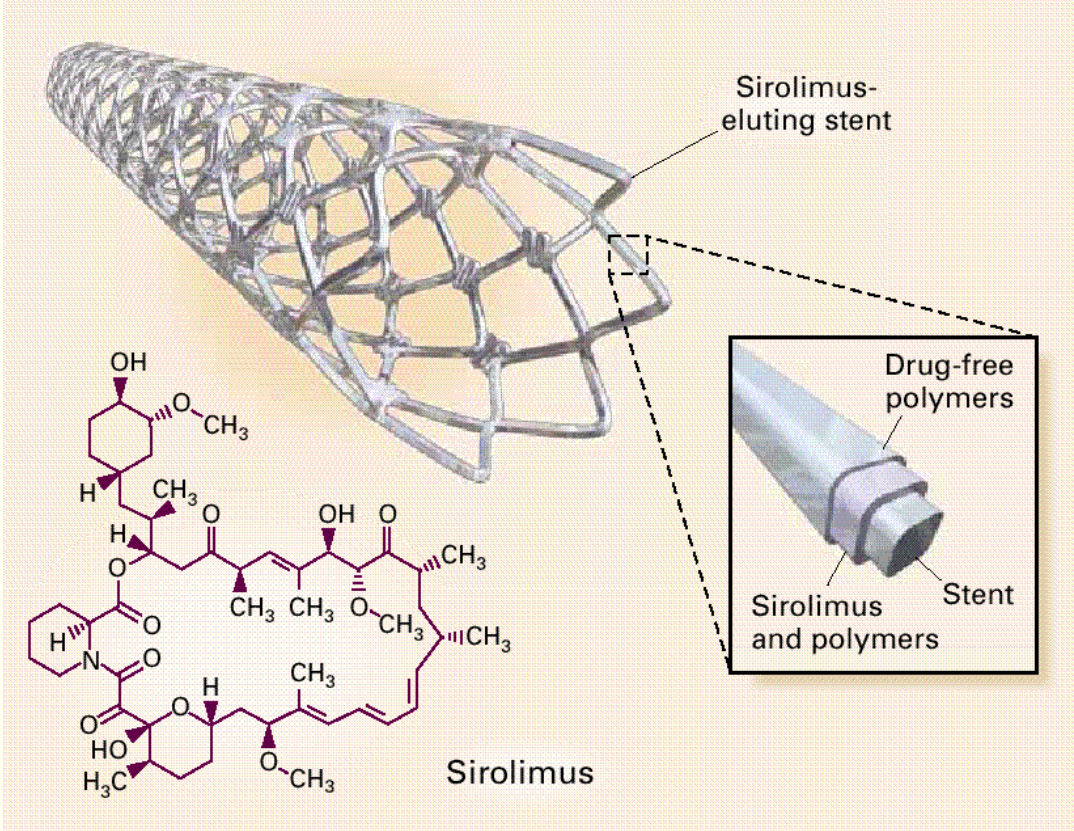
*Note: There are regulations on the requirements for fixed drug-drug combinations found at 21§300.50)

Drug-Eluting Stent

Example: **Cordis' Cypher™ Sirolimus-Eluting Coronary Stent**



Components

- Stent Platform & Delivery System
- Carrier(s)
- Drug