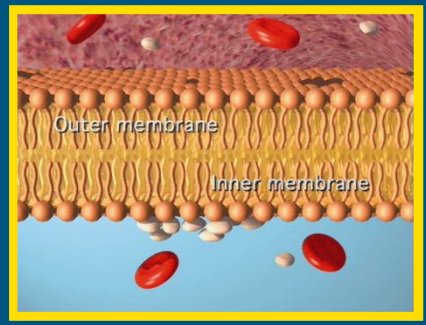
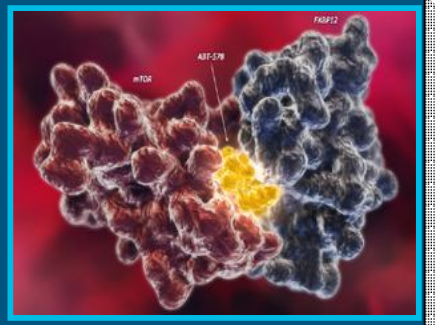
# Industry Experience Sharing

Obtaining Approval for a Combination Product (Drug Eluting Stent)
- in the United States and Chinese Taipei

Gerardine Finn
VP Coronary and RDN Regulatory Affairs
Medtronic

2012 APEC-AHC-AHWP Joint Workshop
- Medical Device Combination Products
November 4, Taipei

# Endeavor Drug-Eluting Coronary Stent System

| STENT TECHNOLOGY | DELIVERY SYSTEM | POLYMER TECHNOLOGY | DRUG |
|---|---|---|---|
|  |  |  |  |
| Driver Cobalt Alloy Stent | Delivery System | PC Technology | Drug: zotarolimus |

Medtronic

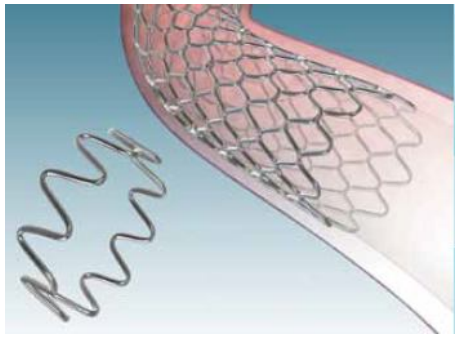
# Stent/Delivery System: Driver/Micro-Driver

**Design:**

- Cobalt Chromium modular stent
- Rapid Exchange (RX), Over-The-Wire (OTW), and Multi Exchange II (MX2) Delivery Systems

**US Approval Status:**

- Bare Metal Stent and Delivery systems approved via PMA October, 2003 /April, 2006



Medtronic

# Polymer Technology

**Design:**

- Biocompatible PC Polymer

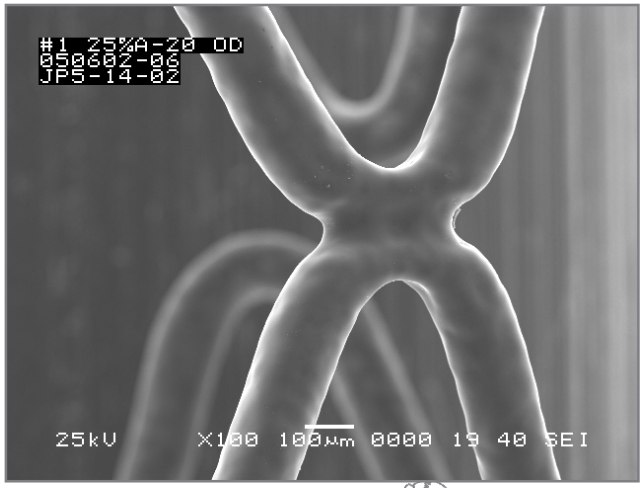
**Status**

- Previously approved on Abbott's Bio*div*Ysio PC coated stent
- Implanted in over 150,000 patients world wide

**US Approval Status:**

- Safety established via prior

  PMA Sept, 2000




Medtronic

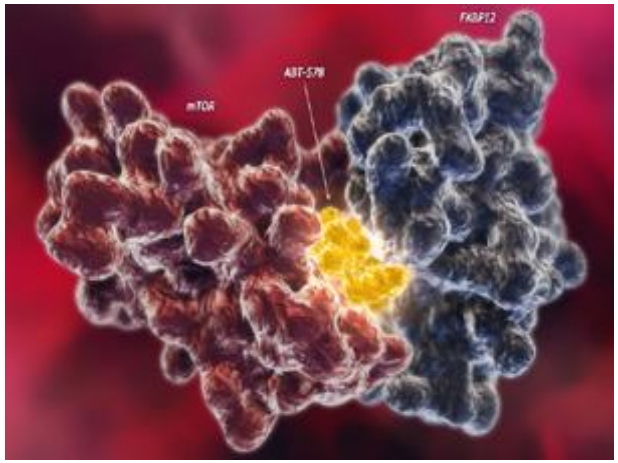
# Drug: Zotarolimus

**Design:**

- New Molecular Entity

**Status:**

- Not previously approved as a drug anywhere in the world




Medtronic

# FDA MANAGEMENT OF COMBINATION PRODUCTS

Medtronic

# Combination Products

- Combination Products defined in 21 CFR Part 3
- Lead Center assigned through Request for Designation (RFD) Process
- Office of Combination Products (OCP) decision is based on Primary mode of action
  - Lead Center for drug-eluting stents (DES) is CDRH
  - CDER provides significant consultation

Medtronic

# FDA Requirements for Drug Eluting Stents

Medtronic

# FDA Requirements for Drug Eluting Stents

- No specific FDA DES guidance when the Endeavor Drug Eluting stent PMA was filed
- FDA guidance subsequently released:

  *"Guidance for Industry: Coronary Drug-Eluting Stents — Nonclinical and Clinical Studies"*

Medtronic

# FDA Considerations for the Endeavor DES

- Data available on components
  - Has the drug component been
    - Approved for the same indication (i.e., on a DES)?
    - Approved for a different indication?
    - Studied for a different indication?
      - ➢ Not studied in humans
  - What is known about the polymer (if present)?
      - ➢ Master file (also, previously reviewed in support of a PMA Sept, 2000)
  - Is the stent platform (scaffold) approved in a bare metal (uncoated) version?
      - ➢ Yes

Medtronic

# FDA Data Requirements for the Endeavor DES

- Full characterization of product
- Bench testing
  - Functional evaluation of stent and delivery system, including coating integrity and particulate matter
- CMC
  - Descriptions of manufacturing and QC for drug component and finished DES
  - Stability studies
- Animal studies
  - Safety studies: clinical dose, overdose (for safety margin)
  - PK - blood and tissue levels

Medtronic

# FDA Data Requirements for the Endeavor DES (continued)

- Since Endeavor DES is comprised of a **New Molecular Entity (NME)*** , data on a minimum of 2000 patients is required to look for rare (<1%) safety events
  - Patients can come from different clinical trials
  - Registry and Randomized Controlled Trial data acceptable
  - Data from International markets outside the US accepted

* **New Molecular Entity (NME):** An active ingredient that has never before been marketed in the United States in any form.

Medtronic

# Endeavor DES Clinical Data

Medtronic

# Endeavor Clinical Program (>2000 patients) Pre PMA Approval

| | | DATA SOURCE |
|---|---|---|
| ENDEAVOR I | Single Arm First-in-Man (n=100) | OUS |
| ENDEAVOR II | 1:1 RCT vs. BMS (E=598,D=599) PK (n=106) | OUS |
| ENDEAVOR II CA | Continued Access Single Arm (n=296) | OUS |
| ENDEAVOR III | 3:1 RCT vs. Cypher® (E=323,C=113) | US |
| ENDEAVOR IV | 1:1 RCT vs. Taxus® (E=773,T=775) | US |
| ENDEAVOR PK | Pharmacokinetic Study (n=43) | US |

- Additional drug only studies were also performed prior to incorporation into Endeavor DES

Medtronic

# Post- FDA Approval Studies On the Endeavor DES

| | | DATA SOURCE |
|---|---|---|
| PROTECT | 1:1 RCT vs Cypher (E=4400,D=4400) | OUS |
| PROTECT CA | Continued Access Single Arm (n=1000) | US |
| EDUCATE DAPT Registry | Multicenter registry ( n= 2500 ) | US |

Medtronic

# Endeavor US Approval Timeline

- IDE filed on Nov 19th 2003

- Final module of PMA submission filed Nov 16th 2006

- Panel Meeting held October 10th 2007

- PMA approval obtained Feb 1st 2008

Medtronic

# FDA REQUIREMENTS FOR SECOND GENERATION DES

Medtronic

## For Second Generation DES, FDA Clinical Requirements vary, and Differ from those of First Generation DES …

- Depend upon the nature of the change

- Defined in the FDA DES guidance document *"Guidance for Industry: Coronary Drug-Eluting Stents - Nonclinical and Clinical Studies"*

Medtronic

# FDA Requirements for Design Modifications to DES

- Minor changes do not require clinical data
- Iterative modifications from currently approved DES may be supported by a small clinical study if safety and efficacy cannot be fully addressed by pre–clinical data
- For a novel DES (e.g. DES with a modified elution profile) a study which supports superiority or non-inferiority against an appropriate control is required

Medtronic

# FDA Requirements for Design Modifications to DES (continued)

- Once a NME is approved in a DES it is no longer regarded as “new” by FDA. Therefore requirements for NME e.g. 2000 patient clinical data no longer apply to next generation devices

Medtronic

# Experiences Gained

- CDRH plays the leading role throughout the entire IDE/PMA process, coordinates all planning and timelines with CDER drug review team, leads detailed review, acts as the primary contact with the sponsor, organizes panel meeting, grants the final PMA approval.
- Endeavor DES is a good example of a highly interactive and collaborative review process between the applicant and reviewers ultimately leading to PMA approval
  - Face-to-face discussions or teleconference meetings throughout process
  - Regular check-ins to discuss application status and review team progress
  - To enable interactive review, efficient and flexible way of accepting responses to deficiency letters
  - Pre-submission meetings between the regulatory agency and applicant are strongly recommended to help to establish requirements or ensure clarification of existing regulation
  - Collaborative pre-PMA planning and discussion per Modular guidance

Medtronic

# Experiences Gained (continued)

- Meeting minutes approved by FDA help to ensure a common understanding of requirements
- Early communication helps set expectations regarding review process and timelines
- International clinical data can be utilized to support US approval
- Data from a single arm study using a historical control or a pre-set Performance Goal (PG) may be acceptable. RCT data is not always required
- US and International clinical studies support post approval requirements

Medtronic

# Endeavor review/approval process in Chinese Taipei

# Background Information

- No specific  DES guidance when the Endeavor Drug Eluting stent was filed
- Bare Metal Stent and Delivery systems (Driver/Micro-Driver ) approved in May 4, 2004
- Drug (Zotarolimus) not previously approved as a drug

Medtronic

# TFDA Requirements & Medtronic Compliance

## ① Manufacturing Facility Registration (QSD)

- QSD registration reviewed by Bureau of Pharmaceutical Affairs (BoPA) ➡ Approved May 2005

## ② Product Registration ➡ Filed January 2006

- ***Device***
  - New Medical Device registration reviewed by BoPA
- ***Drug*** *(no clear combination product rules)* ➡ Filed consultation to BoPA in Sept 2005; Submitted Bridging Study Evaluation in March 2006
- Bridging Study reviewed by Center of Drug Evaluation.

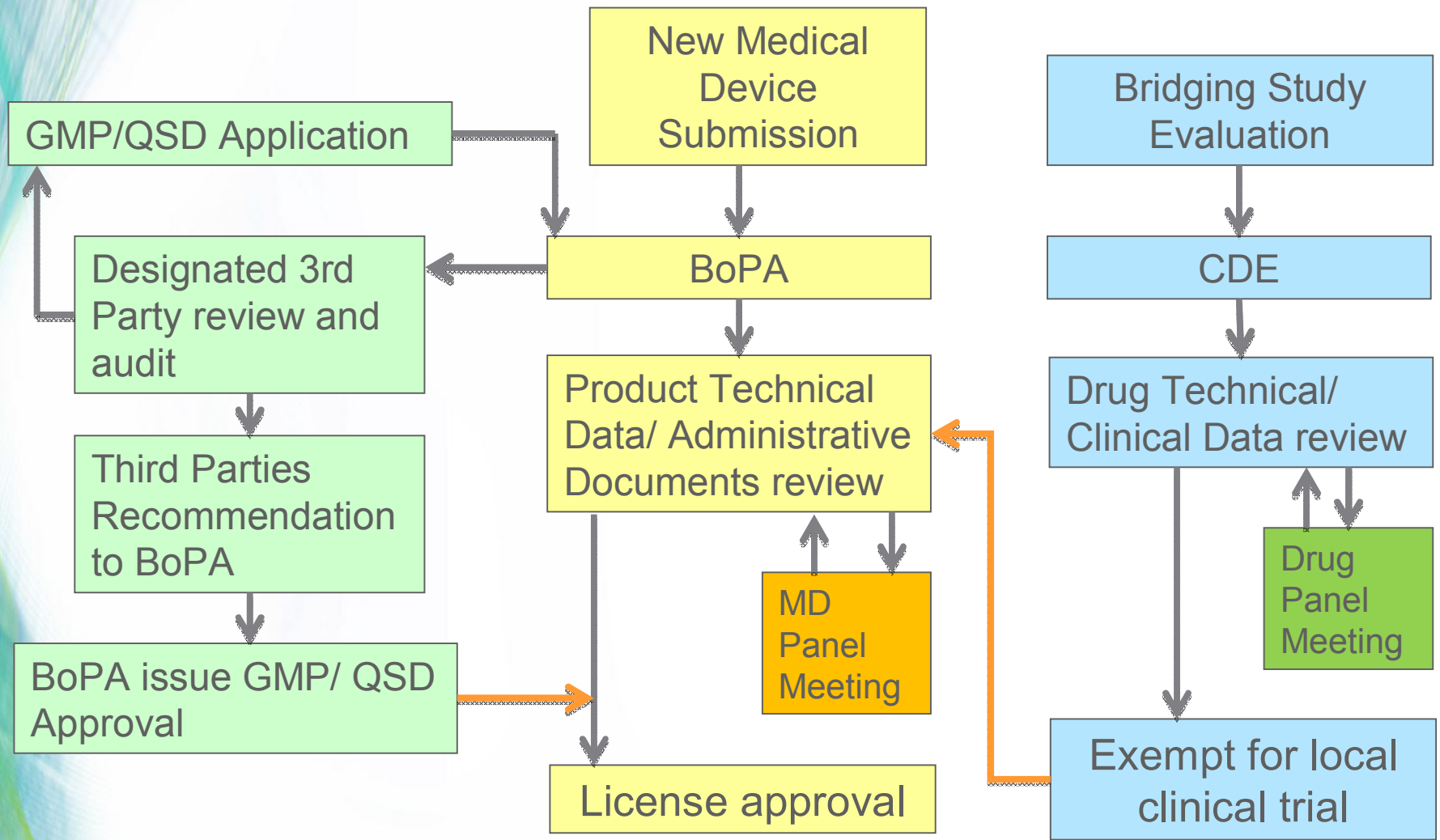
  ➡ Obtained exemption for local clinical study in July 2006

  ➡ Approved in November 2006

**＊THREE submission/ review processes ＊**

Medtronic

# DES review/ approval flowchart




Medtronic

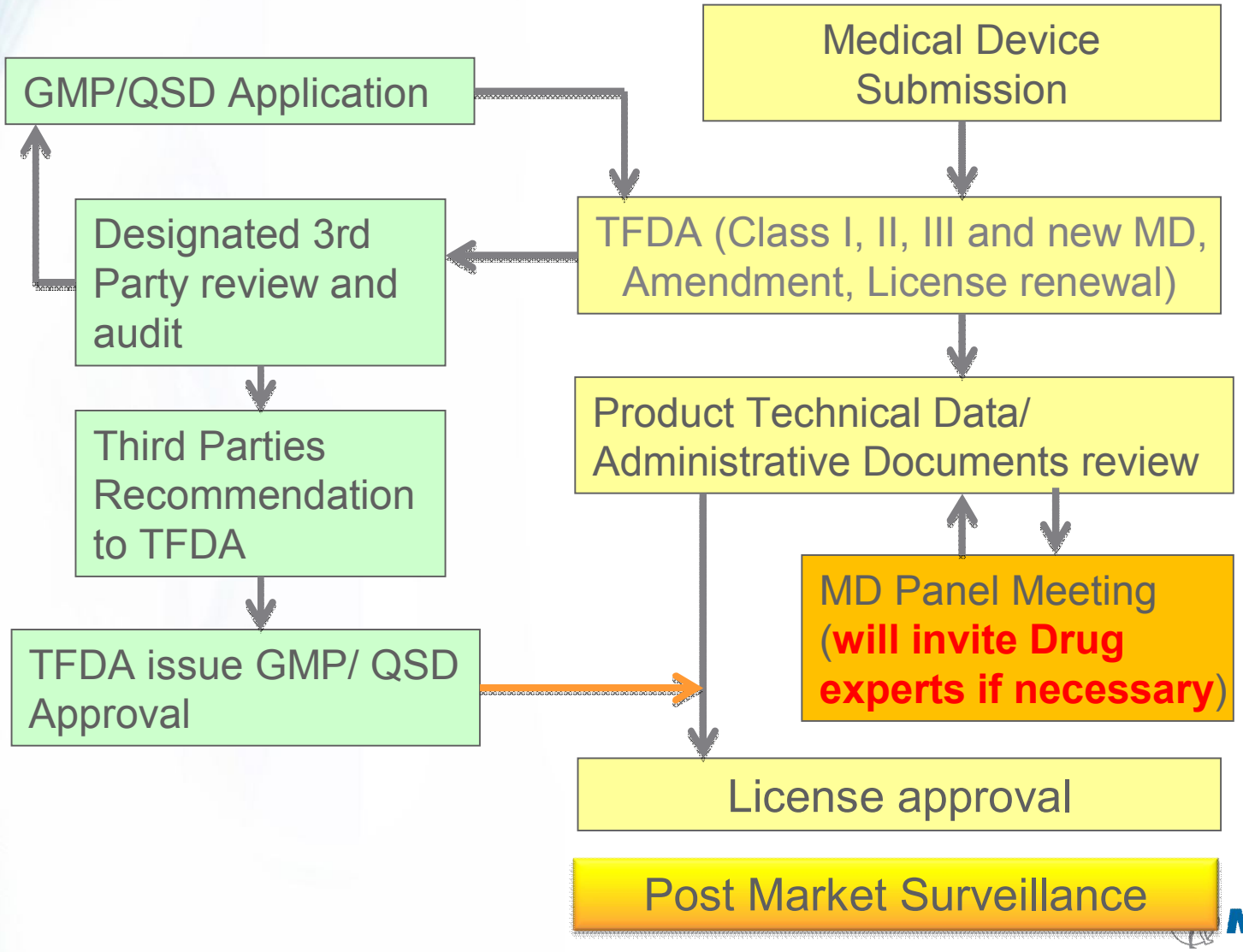
# Update on TFDA Requirements for DES

# Regulatory Environment Changes

- Post Market Surveillance requirement for DES's released on May 9, 2007
- TFDA established in Jan. 1, 2010. Single authorities for Drug, Medical Device, Food, Cosmetics
- TFDA Medical Device Equivalence Evaluation Procedure released on July 8, 2010
- TFDA Guidance for Drug-Eluting Coronary Stents announced on Jan. 3, 2012

Medtronic

# Revised DES review/ approval flowchart




Medtronic

# TFDA - Non-clinical safety and performance data required for DES

- Stent Dimensional and Functional Attributes
- Coating Characterization
- Delivery System Dimensional and Functional Attributes
- Pharmacology and Toxicity for Drug Substance
  (CMC is required for NME or non-DMF approval)
- Biocompatibility for Stents and Delivery System
- Animal Studies
- Drug Release Kinetic Information
- Sterilization
- Packaging
- Shelf Life

Medtronic

# TFDA – DES Clinical data requirements

- A clinical evaluation report containing clinical data or literature review (performed on the product applied for registration) to support the safety and efficacy of the device
- If the drug substance is not approved a bridging study is required

**Challenges in meeting the requirement**

- Clinical data is required for each DES; But,
- Minor changes to an approved DES do not require clinical data

- Despite the availability of a procedure to evaluate substantial equivalence, interpretation varies

# Conclusions

- Medtronic urges global regulatory agencies including FDA, TFDA, and SFDA etc. to harmonized requirements as much as possible.

- MDT will continue to work with regulators around the world, and organization such as  APEC, AHC, AHWP and AdvaMed to ensure best practices are adopted in the regulation of combination products in every region.

Medtronic