



# **Systems Engineering in a Regulatory Environment: Examples from the Medical World**

**Session B3**

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# Welcome to Session B3!

- Introductions
- Logistics of this session





# Many different worlds of regulation

- International organization for standardization (ISO)
  - From textiles to air quality to management and more
- Department of Defense (DoD)
  - Military and space applications
- Federal Aviation Administration (FAA)
  - Planes, pilots, airports
- Food and Drug Administration (FDA)
  - Food, cosmetics, medical products





# Why 'Regulatory' in Systems Engineering?

- Depending on your product...
  - *Design*
  - *Documentation*
  - *Manufacturing*
  - *Testing and evaluation*
  - *Marketing*
  - *And many other aspects and activities*

Could be REGULATED!





# Why 'Regulatory' in Systems Engineering?

- Important for Systems Engineering concepts and processes
  - Government policy and regulations
  - Marketing
  - Test, measurement, and evaluation
  - Manufacturing
  - Safety and health hazards





## Regulatory “Constraints”

- On the plus side: (i.e. glass is half full)
  - Regulations are usually created with good intentions!
  - May help streamline processes and encourage good practices
  
- But at the same time: (i.e. glass is half empty)
  - Regulations can be overwhelming and confusing
  - May place severe limits on what you can do





# Today's Focus: Medical Devices

- Medical products are highly regulated
  - Sometimes dealing with hazardous materials (biologics, chemicals, radiation)
  - Even inert products may pose great risks
  
- Regulations impact nearly all stages of product life cycle and many employees in a company
  - *We will use medical devices as our example for today*





# Objectives

- **At the end of this session, you should be able to:**
  - Discuss the relevance of regulatory constraints to Systems Engineering
  - Describe a specific example of how federal regulations impact medical devices
  - Seek out information on regulations in your specific field of interest





# The FDA and Medical Devices...





# Food and Drug Administration

- Federal regulatory agency
  - Regulates products in the United States
  - Within executive branch of US government
    - Under Dept of Health and Human Services
  
- Role of the FDA: Promote public health by reviewing clinical research and taking appropriate action on the marketing of **regulated products**





# Food and Drug Administration

- Products regulated by the FDA include:
  - all foods except for meat and poultry
  - prescription and non-prescription drugs
  - blood products
  - vaccines
  - tissues for transplantation
  - medical devices
  - radiological products (including cellular telephones)
  - animal drugs and feed
  - cosmetics





# FDA and Medical Devices

- If you want to use or sell your medical device in the United States, the FDA will regulate it!
  - “Device” can be as simple as tongue depressor or thermometer, or as complex as an artificial heart
- Specific center within the FDA for medical devices:  
Center for Devices and Radiological Health (CDRH)  
*Other products, such as drugs or cosmetics, are the focus of other centers*



# All Devices Created Equal?

- No!!
- Device classification system- each device regulated based on risk
  - Riskiest devices subject to highest regulatory scrutiny and control
  - Foundation of premarket approval and clearance
- **Classifications:** “risk” related to intended use, materials, complexity, potential harm, clinical familiarity
  - Class I: minimum regulation- Ex: cane, ear cannula, tongue depressor
  - Class II: moderate- Ex: infusion pump, powered wheelchair, condom
  - Class III: most stringent- Ex: defibrillator, stent, artificial hip



# Device Classifications

- Extent of regulation depends on classification of device
  - Class I: Subject to General Controls (QSR's)
  - Class II: QSR's and Special Controls
  - Class III: Premarket Approval Required
  
- All classes subject to Quality Systems Regulation
  - Good Manufacturing Practices for medical devices





# Quality Systems Regulation (QSR)

- Major subparts
  - A. General Provisions
  - B. Quality System Requirements
  - C. Design Controls
  - D. Document Controls
  - E. Purchasing Controls
  - F. Identification and Traceability
  - G. Production and Process Controls
  - H. Acceptance Activities
  - I. Non-Conforming Product
  - J. Corrective and Preventive Action
  - K. Labeling and Packaging Control
  - L. Handling, Storage, Distribution and Installation
  - M. Records
  - N. Servicing
  - O. Statistical Techniques





# Quality Systems Regulation (QSR)

- FDA requires components of QSR- but does not specify how to establish the system within each company
  - Up to the organization to decide
  - Subcontractors must comply with QSR also!
- Many roles within a company are affected by QSR
  - Executive management included



# More Device Regulation

- Class II and III devices are regulated by more than just QSR
  - Special controls or premarket approval may require additional evaluation- all of which is regulated
    - Specified bench testing
    - Animal studies
    - Clinical trials
  - *Aimed at supporting safety and effectiveness of devices that are put on the market*



# More Device Regulation

*Disclaimer: No regulatory mechanism can guarantee that a product will never cause injury or will always be effective*





# FDA Regulation: Paths to Market

- 510k
  - “Me too” – substantially equivalent to existing product
  - Class I, II (unless exempt)
  - Process relatively short and less costly
  - Product receives clearance for market
- Premarket Approval (PMA)
  - Unique, more complex devices
  - Class III
  - Process relatively lengthy and costly
  - Product receives approval to market





*Any preclinical or clinical testing that is performed as part of 510k or PMA pathways must adhere to regulations and guidelines*



# Preclinical Testing and Evaluation

- Bench and in vitro testing
  - Goal: to evaluate chemical properties, mechanical properties, biocompatibility, etc.
  - Regulations
    - Many are performed based on ISO specifications
    - Performed according to Good Laboratory Practices
      - “GLP”= another set of regulations and guidelines



# Preclinical Testing and Evaluation

## ■ Animal studies

- Goal: to test a new device in animal models -primarily to show safety

- Regulations

- Approvals and protocols through an Institutional Animal Care and Use Committee (IACUC)
- Performed according to Good Laboratory Practices

## ■ *FDA Guidance Documents: provides resource for navigating regulatory path for specific products*



<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfggp/search.cfm>





# Clinical Studies

- Following proper evidence that supports the safety of a device...
  - ...it's time to evaluate the product in humans
  - ...and of course this is strictly regulated as well
- Goal: to determine safety and effectiveness in a patient population
  - Regulations
    - Must receive "Investigational Device Exemption" from FDA
    - Requires oversight by Institutional Review Board (IRB)
    - Must adhere to Good Clinical Practices





# Eventually and Hopefully

- Submit application to receive clearance or approval from the FDA to market your product
- And if you get the thumbs-up...



# Post-Market Compliance

- Regulations don't go away once your product is approved or cleared for market
  - Manufacturing facility audits
  - Promotional advertising and labeling
  - Reports and follow-ups
  - Recalls and field corrections
  - Supplements and changes

# Summary

- Medical Device Regulation:
  - The FDA will regulate
    - How your device must be tested before entering the marketplace
    - How your device is manufactured and distributed
    - How your device is labeled for use
    - How your device is tracked and evaluated over time
    - And more!
  
- ***To get to market, you must understand how your device will be classified and how regulations apply!!***

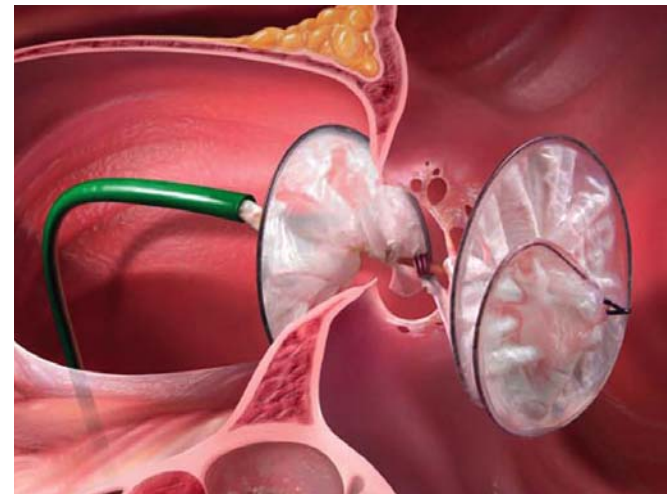
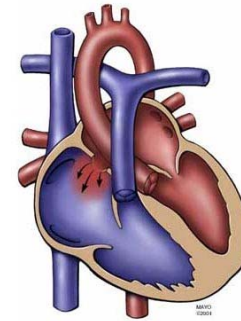


# BREAK



# CASE STUDY: Gore Helex

- Catheter-delivered device to close atrial septal defects
- Alternative to invasive surgery
- Composed of ePTFE, nitinol frame, and catheter system





# CASE STUDY: Gore Helex

- Gore's path to market from a regulatory standpoint...
- Class III medical device
- Needed Premarket Approval from FDA





# CASE STUDY: Gore Helex

- Quality Systems Regulation
- Bench testing (examples)
  - Hardness and fatigue testing of nitinol wire
  - Tensile strength of ePTFE
  - Reliability of device deployment
- In vitro testing (examples)
  - Cytotoxicity and hemocompatibility testing
    - ISO Biocompatibility standards



# CASE STUDY: Gore Helex

- Animal testing
  - Canine model with surgically created septal defects
  - Assessed:
    - Device placement and repositioning
    - Time for implantation and “efficacy” (i.e. closure rate)
    - Evidence of thrombus or remote thromboemboli
    - Wear and fatigue
    - Cell/EC incorporation
  - **Successful completion of animal studies supported initiation of human clinical trials**



# CASE STUDY: Gore Helex

## ■ Clinical studies

- Gore received informed consent from all patients
  - Had to provide information including: purpose of research, duration of studies and participation, description of procedures, foreseeable risks or discomforts, description of benefits, disclosure of alternatives, compensation, etc.
  
- Performed initial feasibility study in April 2000





# CASE STUDY: Gore Helex

## ■ Clinical Studies

- Expanded to multicenter pivotal study in March 2001
- Continued access study in 2003 evaluated device modifications

*Conclusions: Gore Helex is “not inferior” to surgical closure and is a reasonably safe and effective treatment for atrial septal defects*





# CASE STUDY: Gore Helex

- Putting it all together in a submission to the FDA...
  - Summary is available: <http://www.fda.gov/cdrh/pdf5/P050006.html>
- Approval
  - Based on combo of in vitro, bench, animal, and clinical data:
    - **Notice of Approval issued from FDA in August '06**
    - **...Subject to labeling changes and 5-year follow-up**



# CASE STUDY: Gore Helex

## ■ Post-Approval:

New Search	New Search	New Search	New Search <a href="#">Back To Search Results</a>
<p>Note: this medical device record changed. Be sure to look at th device.</p>	<p>Note: this medical device record is changed. Be sure to look at the <a href="#">ori</a> device.</p>	<p>Note: this medical device record is changed. Be sure to look at the <a href="#">ori</a> device.</p>	<p>Note: this medical device record is a supplement. The device description may have changed. Be sure to look at the <a href="#">original PMA</a> to get an up-to-date view of this device.</p>
<b>Premarket</b>	<b>Premarket App</b>	<b>Premarket App</b>	<b>Premarket Approval (PMA) Database</b>
<p><b>Trade Name</b></p> <p><b>Classification Name</b></p> <p><b>Generic Name</b></p> <p><b>Applicant</b></p> <p><b>PMA Number</b></p> <p><b>Supplement Number</b></p> <p><b>Date Received</b></p> <p><b>Decision Date</b></p> <p><b>Product Code</b></p> <p><b>Advisory Committee</b></p> <p><b>Supplement Type</b></p> <p><b>Supplement Reason</b></p> <p><b>Expedited Review Granted?</b></p> <p><b>Approval Order Statem</b></p>	<p><b>Trade Name</b></p> <p><b>Classification Name</b></p> <p><b>Generic Name</b></p> <p><b>Applicant</b></p> <p><b>PMA Number</b></p> <p><b>Supplement Number</b></p> <p><b>Date Received</b></p> <p><b>Decision Date</b></p> <p><b>Product Code</b></p> <p><b>Advisory Committee</b></p> <p><b>Supplement Type</b></p> <p><b>Supplement Reason</b></p> <p><b>Expedited Review Granted</b></p> <p><b>Approval Order Statement</b> procedure for the nitinol wire</p>	<p><b>Trade Name</b></p> <p><b>Classification Name</b></p> <p><b>Generic Name</b></p> <p><b>Applicant</b></p> <p><b>PMA Number</b></p> <p><b>Supplement Number</b></p> <p><b>Date Received</b></p> <p><b>Decision Date</b></p> <p><b>Product Code</b></p> <p><b>Advisory Committee</b></p> <p><b>Supplement Type</b></p> <p><b>Supplement Reason</b></p> <p><b>Expedited Review Granted?</b></p> <p><b>Approval Order Statement</b> the catheter delivery system (</p>	<p><b>Trade Name</b></p> <p><b>Classification Name</b></p> <p><b>Generic Name</b></p> <p><b>Applicant</b></p> <p><b>PMA Number</b></p> <p><b>Supplement Number</b></p> <p><b>Date Received</b></p> <p><b>Decision Date</b></p> <p><b>Product Code</b></p> <p><b>Advisory Committee</b></p> <p><b>Supplement Type</b></p> <p><b>Supplement Reason</b></p> <p><b>Expedited Review Granted?</b></p> <p><b>Approval Order Statement</b></p>
			<p>GORE HELEX SEPTAL OCCLUDER</p> <p><a href="#">Occluder, Transcatheter Septal</a></p> <p>Septal Occluder</p> <p>W.L. GORE &amp; ASSOCIATES,INC</p> <p>P050006</p> <p>S005</p> <p>11/06/2007</p> <p>12/06/2007</p> <p>MLV [<a href="#">Search Manufacturers For MLV</a>]</p> <p>Cardiovascular</p> <p>30-day Notice</p> <p>Process Change: Manufacturing</p> <p>No</p> <p>Adoption of an electronic verification system (evs) to be used in the packaging of the device.</p>

# Other Complicating Issues

- What about reimbursement?
  - FDA approval does not always mean Medicare reimbursement
    - If no one will pay for it, does it matter whether FDA approved it?
    - *Reimbursement strategy should be considered early on in the regulatory approval process*

# Other Complicating Issues

- What if it's a combination product?
  - (i.e. a device coated with a drug)
  
- Product will go through FDA's Office of Combination Products
  - Working with new test methods, new manufacturing, and a whole new regulatory world
  - Development timelines increase!

# Other Complicating Issues

## ■ What about the rest of the world?



- FDA regulations and approval are specific to the U.S. market
- If you want to market your product in:
  - Europe, China, Australia, Canada, etc.
  - ***It's another regulatory process!!***



# The Good News...





# Role of the Regulatory group

- Within a company there is usually a regulatory affairs group
  - Develops regulatory strategy
  - Advises and participates in product team meetings
  - Reviews documents and prepares submissions
  - Interacts with regulatory bodies
  - Prepares and submits documentation for changes
  - Assists with product reporting and tracking



# Summary and Conclusions

- Product development in a regulatory setting requires organization, documentation, and adherence to many guidelines
- For medical devices in the US:
  - Design, testing, in vivo evaluation, manufacturing, labeling, and other facets are regulated by the FDA
- For any regulated product, awareness of regulatory constraints is necessary part of Systems Engineering

## Some useful links

- Food and Drug Administration (FDA)
  - <http://www.fda.gov/> (main page)
  - <http://www.fda.gov/cdrh/devadvice/> (medical devices)
  
- Federal Aviation Administration (FAA)
  - [http://www.faa.gov/regulations\\_policies/](http://www.faa.gov/regulations_policies/)
  
- ISO Standards
  - <http://www.iso.org/iso/home.htm>



# Summary and Conclusions

- Revisit Objectives:
  - Discuss the relevance of regulatory constraints to Systems Engineering
  - Describe a specific example of how federal regulations impact medical devices
  - Seek out information on regulations in your specific field of interest

