Lecture 16: Standards and Regulations

International Standards

- Industry + regulation + academia develop standards
- Regulation agencies adopt/recognize standards
- Software companies comply to standards
- Standards emphasize communication and shared understanding
  - For example: if one person says, "*Testing is complete*", will all affected bodies understand what those words mean?
- less time is spent on non-productive work

Benefits of Standards

- Encapsulation of best practice
  - avoids repetition of past mistakes
- Framework for quality assurance process
  - it involves checking standard compliance
- Provide continuity
  - new staff can understand the organisation by the standards applied

Problems with standards

- Small software organizations perceive them as being orientated towards large organizations.
- Negative views of cost, documentation and bureaucracy
- Difficult to relate standards to their business needs and to justify the application of the international standards in their operations

Who is the ISO?

- International Organization for Standardization
  - world's largest developer of International Standards
- A network of the national standards institutes of 162 countries, one member per country
- ISO is a non-governmental organization that forms a bridge between the public and private sectors
  - Many of its member institutes are part of the governmental structure of their countries, or are mandated by their government
  - Other members have their roots uniquely in the private sector, having been set up by national partnerships of industry associations
- This enables ISO to reach a consensus on solutions that meet both the requirements of business and the broader needs of society

Who develops ISO standards

- By technical committees, (or subcommittees) comprising experts from the industrial, technical and business sectors
- These experts may be joined by representatives of government agencies, consumer associations, non-governmental organizations and academic circles, etc.
- Experts participate as national delegations, chosen by the ISO national member body for the country concerned.

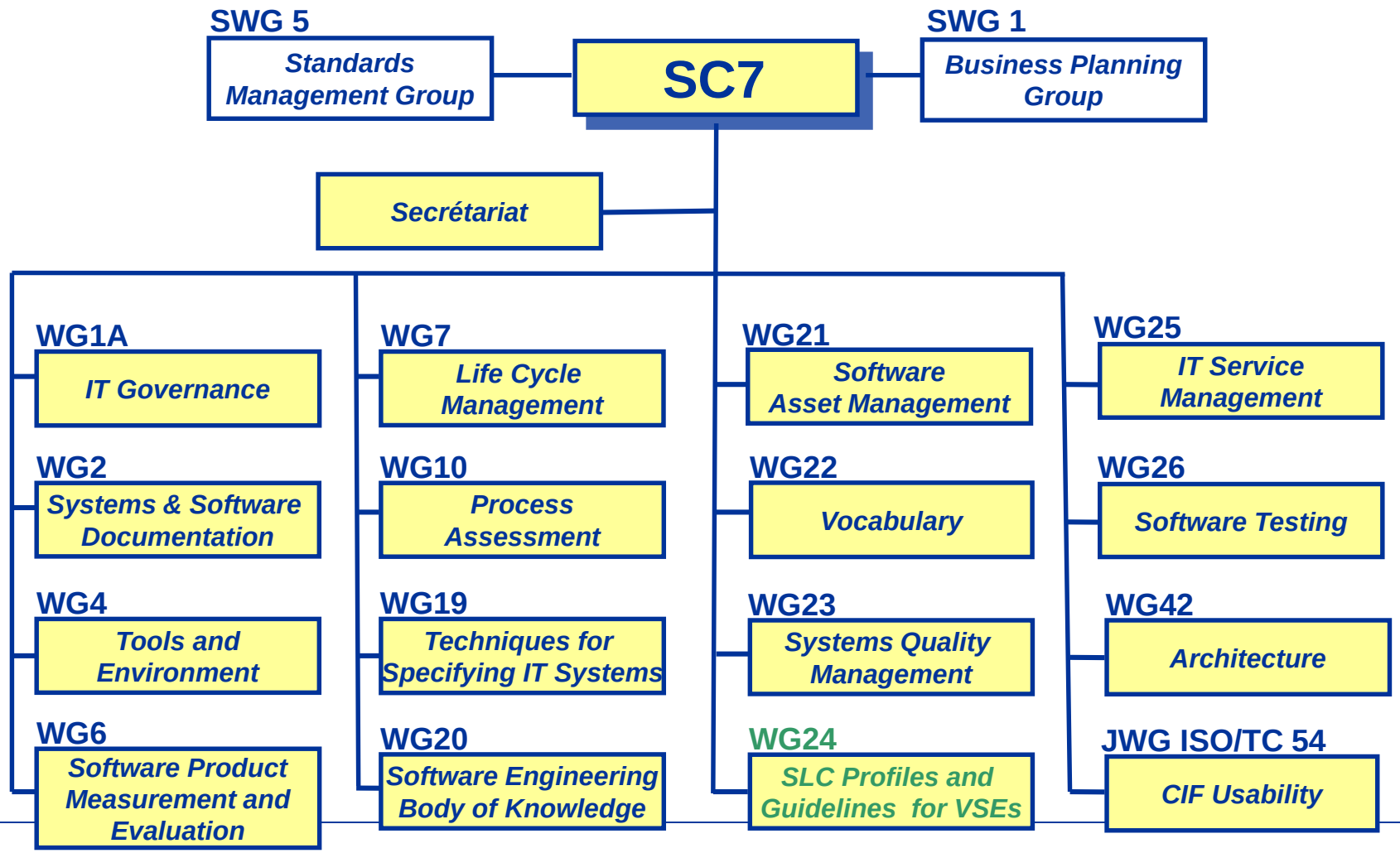
How ISO standards are developed

- The national delegations of experts of a committee meet to discuss, debate and argue until they reach consensus on a draft agreement
- The resulting document is circulated as a Draft International Standard (DIS) to all ISO's member bodies for voting and comment
- If the voting is in favor, the document, with eventual modifications, is circulated to the ISO members as a Final Draft International Standard (FDIS)

ISO/IEC JTC 1 SC7

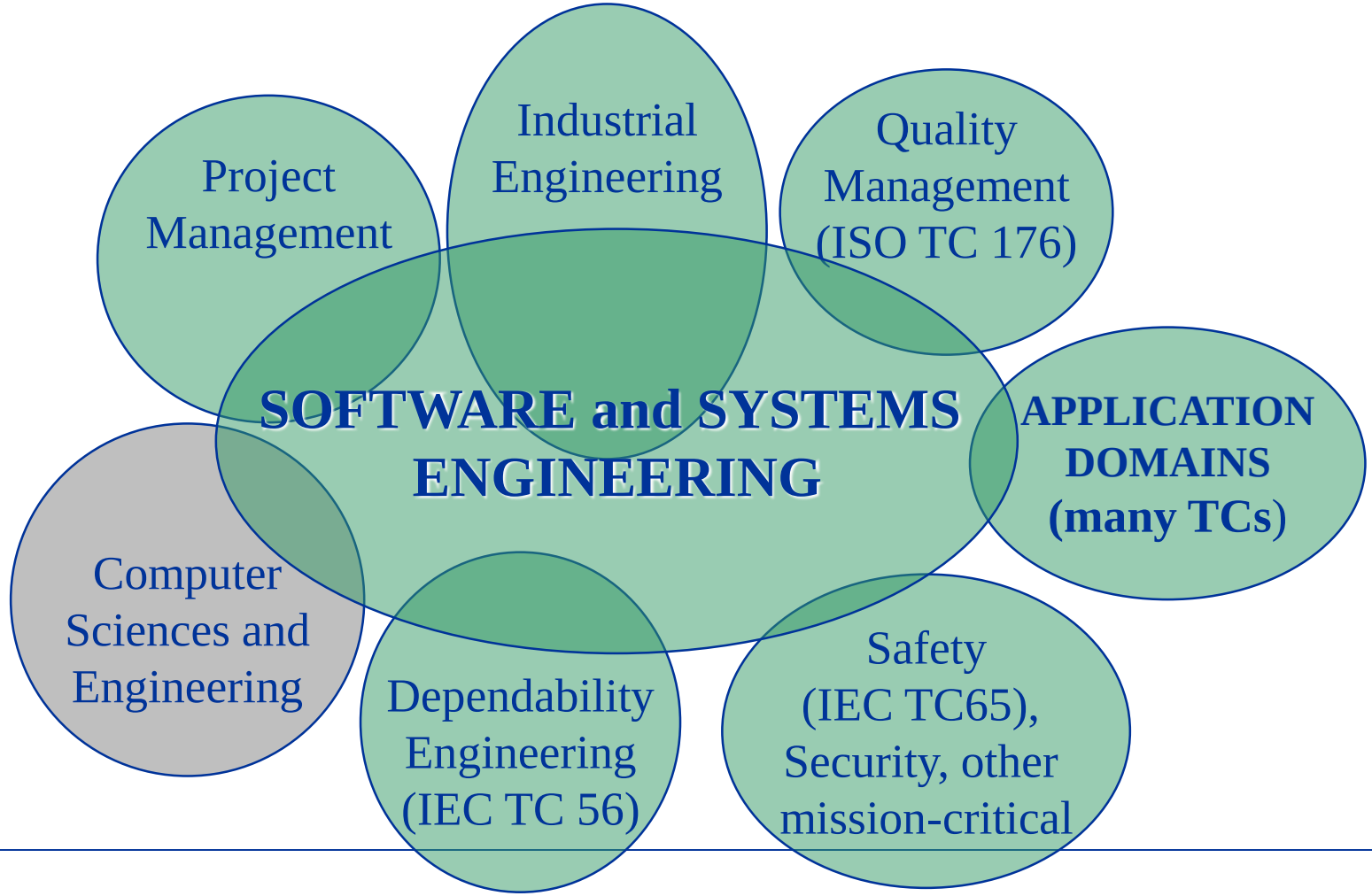
- ISO/IEC JTC 1 SC7
  - International Organization for Standardization/ International Electrotechnical Commission Joint Technical Committee 1 Sub-Committee 7
- ISO/IEC JTC 1 SC7 Terms of Reference
  - “Standardization of processes, methods and supporting technologies for the engineering and management of software and systems throughout their life cycles”

SC7 Structure



‡ Adapted from Prof. M. Azuma

Domains covered by SC7



Software Engineering Related Standards

- *Software-Development Standards*
  - *IEEE Std 830, Recommended Practice for Software Requirements Specifications*
  - *IEEE Std 1233, Guide for Developing System Requirements Specifications*
  - *IEEE Std 1016, Recommended Practice for Software Design Descriptions*
  - *IEEE Std 828, Standard for Software Configuration Management Plans*
  - *IEEE Std 1063, Standard for Software User Documentation*
  - *IEEE Std 1219, Standard for Software Maintenance*

Software Engineering Related Standards

- *Software Quality-Assurance Standards*
  - *IEEE Std 730, Standard for Software Quality Assurance Plans*
  - *IEEE Std 1028, Standard for Software Reviews*
  - *IEEE Std 1008, Standard for Software Unit Testing*
  - *IEEE Std 829, Standard for Software Test Documentation*
  - *IEEE Std 1061, Standard for a Software Quality Metrics Methodology*

Software Engineering Related Standards

- *Management Standards*
  - *IEEE Std 1058, Standard for Software Project Management Plans*
  - *IEEE Std 1074, Standard for Developing Software Life Cycle Processes*
  - *IEEE Std 1045, Standard for Software Productivity Metrics*
  - *IEEE Std 1062, Recommended Practice for Software Acquisition*
  - *IEEE Std 1540, Standard for Software Life Cycle Processes - Risk Management*
  - *IEEE Std 1490, Guide - Adoption of PMI Standard - A Guide to the Project Management Body of Knowledge*

Regulated Industries

Regulated industries

- Industries in which the failure of the products may cause social impacts
- Aviation
  - FAA, etc
- Nuclear
- Medical
  - FDA
- Automobile

Conflicting goals of regulators

- Guarantee safety and effectiveness
- Encourage the development and use of new technologies
- Philosophy: Least Burdensome Approach

The goal of medical device certification

- Ensure safety and effectiveness of medical devices
  - Safety: Whether probable benefits to health from use of the device outweigh any probable risks?
  - Effectiveness: Whether the use of the device in the target population will provide clinically significant results

- The Food and Drug Administration (FDA) require safety & efficacy evidence provided by device manufacturers
  - Pre-market
    - Cleared/approved for sale on U.S. market
  - Post-market surveillance
    - Recall flawed devices

What are General Controls?

- Basic authorities that provide FDA with the means to regulate medical devices.

- Applies to all medical devices regardless of classification, are subject to premarket and postmarket regulatory controls.
  - Establishment registration and device listing
  - Premarket notification or 510(k), if not exempt
  - Labeling
  - Misbranding
  - Adulteration
  - Quality Systems
  - Records and Reports / Medical Device Reporting (MDR)

What are Special Controls?

- General controls alone are insufficient to assure safety and effectiveness of certain devices
- Existing methods are available to provide such assurances.
  - **Postmarket Surveillance Study**
  - **Patient Registries**
  - **Guidelines (e.g., Glove Manual)**
  - **Mandatory Performance Standard**
  - **Recommendations or Other Actions**
  - **Special Labeling (e.g., 882.5970, Cranial Orthosis)**

Device classifications

- Whether control regulations can ensure the safety and effectiveness of medical devices

- Class I
  - General controls can ensure safety and effectiveness

- Class II
  - General controls not enough, need special controls

- Class III
  - Insufficient information exists to determine that general and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of such devices

Risk-based Classification

- Classified according to its risks

	Class I	**Class II**	**Class III**
Risk	**Low**	**Medium**	**High**
Clearance/Approval	Not required	Premarket Notification 510(k)	Pre-Market Approval (PMA)
Controls	General Controls	General & Special Controls 510(k) submission	General & Special Controls Premarket Approval (PMA)
Comparison	Not required	Predicate	Clinical Truth
Submission Studies	Not required	Preclinical/Clinical	Preclinical & Clinical
Notation	Marketed	Cleared	Approved

PRE-MARKET NOTIFICATION 510(K)

Substantial Equivalence (SE)

- Prove that the new device is substantially equivalent to a predicate device(s)
- Philosophy: If there exists a device which has been proven to be safe and effective, and your new device is very similar to that device, your device may probably be safe and effective
- Least burdensome principle by FDA
  - Only provide necessary (minimum required) information
  - Balance between risks and medical benefits

Predicate Device(s)

- (i) was legally marketed prior to May 28, 1976 (pre-amendments device) and for which a PMA is not required;
  - "Grandfathered" devices
- or (ii) has been reclassified from Class III to Class II or I;
- or (iii) has been found Substantial Equivalent through the 510(k) process.

Predicate Selection

- Is the predicate device legally marketed?
- Do the devices have the same intended use?
- Do the devices have the same technological characteristics?
- Do the different technological characteristics raise different questions of safety and effectiveness?
- Are the methods of evaluating new/different characteristics acceptable?
- Does the data demonstrate substantial equivalence?

Technological Characteristics

- Materials
- Design
- Energy Source
- Other Features
- Same ≠ Equivalent
  - Does not raise DIFFERENT issues of safety or effectiveness
  - Must be as safe and effective as predicate
  - Example: cutting with knife vs. cutting with laser

Class I / II 510(k) Exemptions

- Over 800 generic types of Class I devices and 60 Class II devices are exempted from the premarket notification requirement (*Federal Register)*

- 510(k) Exempt Devices - approximately 47%

  Class I 93%

  Class II 9%

- Devices exempt from 510(k) are:
  - "preamendment devices" not significantly changed or modified; or
  - Class I/II devices specifically exempted by regulation.

Multiple Predicates

- 1 st Predicate has same intended use
- 2 nd Predicate has same technological characteristics

- This is not allowed.

Multiple Predicates Allowed…

- Evaluated on case-by-case basis
- New performance testing required
- Option 1: Two predicates with different technological characteristics, but the same intended use
  - Example: Hemodialysis catheter
    - Predicate A has same extension design
    - Predicate B has same tip design
    - Both A & B predicates have the same intended use
- Options 2: More than one indication under the same intended use
  - Example: Fracture fixation plate
    - Predicate A is indicated for middle bone fractures
    - Predicate B is indicated for bone tip fractures
    - Both A & B predicates are intended for long bone fractures

A Device is NSE if:

- There is no predicate device; or
- It has a new intended use; or
- It has different technological characteristics compared to the predicate device and it raises a different type question of safety and effectiveness; or
  - Pacemaker programmer Windows update
- It does not demonstrate that it is at least as safe and effective as the predicate.
- Approximately 3%-4%

The Special 510(k) Program

- A modification of your 510(k) cleared device that you own
- The modification does not alter the intended use or the fundamental scientific technology of the device
  - Submit only the documentation related to the modification that prompted the submission

Doubts regarding 510(k)

- A loophole?
  - Most of the new pacemakers nowadays are cleared using 510(k)

PRE-MARKET APPROVAL (PMA)

Pre-Market Approval (PMA)

- Required for most Class III devices
  - Besides pre-amendment devices

- The most stringent type of device marketing application required by FDA

PMA Review Stages

- Pre-Sub meeting with FDA
  - Discuss: Device design Bench testing Animal testing Clinical trial
- Investigational Device Exemption (IDE)
  - Request approval for clinical trial
- PMA
  - Request market approval
- PMA-S
  - Request approval for device change or upgrade (which may require a new IDE)

Data Requirements

- Non-clinical Laboratory Studies Section:
  - Pre-clinical
  - Biocompatibility
  - Stress
  - Animal Tests
- Clinical Investigations Section:
  - Study protocols
  - Safety and effectiveness data
  - Adverse reactions and complications
  - Device failures and replacements
  - Patient information
  - Results of statistical analyses

institutional review boards (IRBs)

- An appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects.
- Has the authority to approve, require modifications in (to secure approval), or disapprove research
- Determine whether a device study
  - Significant Risk (SR) Device Studies
    - Requires Investigational Device Exemption (IDE) application to FDA
  - Non-significant Risk (NSR) Device Studies

WHAT SHOULD IRBS CONSIDER WHEN MAKING THE SR AND NSR DETERMINATION?

- What is the basis for the risk determination?
  - based on the proposed use of a device in an investigation, and not on the device alone.
- What is the nature of harm that may result from use of the device?
  - Potential serious risk to the health, safety, or welfare of a subject
- Will the subject need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure?

SR & NSR Study Examples

- A new pacemaker lead
  - SR, since additional procedure is needed
- Extended wear contact lens
  - SR, wearing the lens overnight pose additional risks
- Daily wear lenses
  - NSR

Investigational Device Exemption (IDE)

- Allows the investigational device to be used in a significant risk clinical study
- Can be used to collect safety and effectiveness data to support a PMA or a 510(k) submission
  - most often conducted to support a PMA
- Risk to patient balanced by anticipated benefits
- Device labeled for investigational use only

Type of IDEs

- Feasibility study
  - May provide support for a future pivotal study or may be used to answer basic research questions
  - Not intended to be the primary support for a marketing application
  - Endpoints and sample size generally not statistically driven
  - Often required by FDA prior to pivotal study to assess basic safety and potential for effectiveness
  - Generally ~10-40 patients but may be larger
  - FDA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk

Type of IDEs

- Pivotal study
  - Generally intended as the primary clinical support for a marketing application
  - Designed to demonstrate a “reasonable assurance of safety and effectiveness”
  - Endpoints and sample size statistically driven
  - Designed to assess both safety and effectiveness
  - FDA review is much more complex

Level of Evidences

- Randomized, multi-arm, “blinded” study
- Randomized, multi-arm, un“blinded” study
- Non-randomized study
- Single-arm study with patient serving as own control
- Single-arm study with Historical Control (using patient-level data)
- Single-arm study with Objective Performance Criteria
- Observational study
- Systematic review (meta-analysis with patient-level data)
- Meta-analysis based on summary information only
- Literature Summary
- Uncertain

Humanitarian Device Exemption (HDE)

- Purpose: approval to market a class III (high risk) device for an unmet need in a patient population
  - Must first obtain designation as a Humanitarian Use Device (HUD) from the Office of Orphan Products (OOP)
- An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA.
- HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of disease affecting these populations.