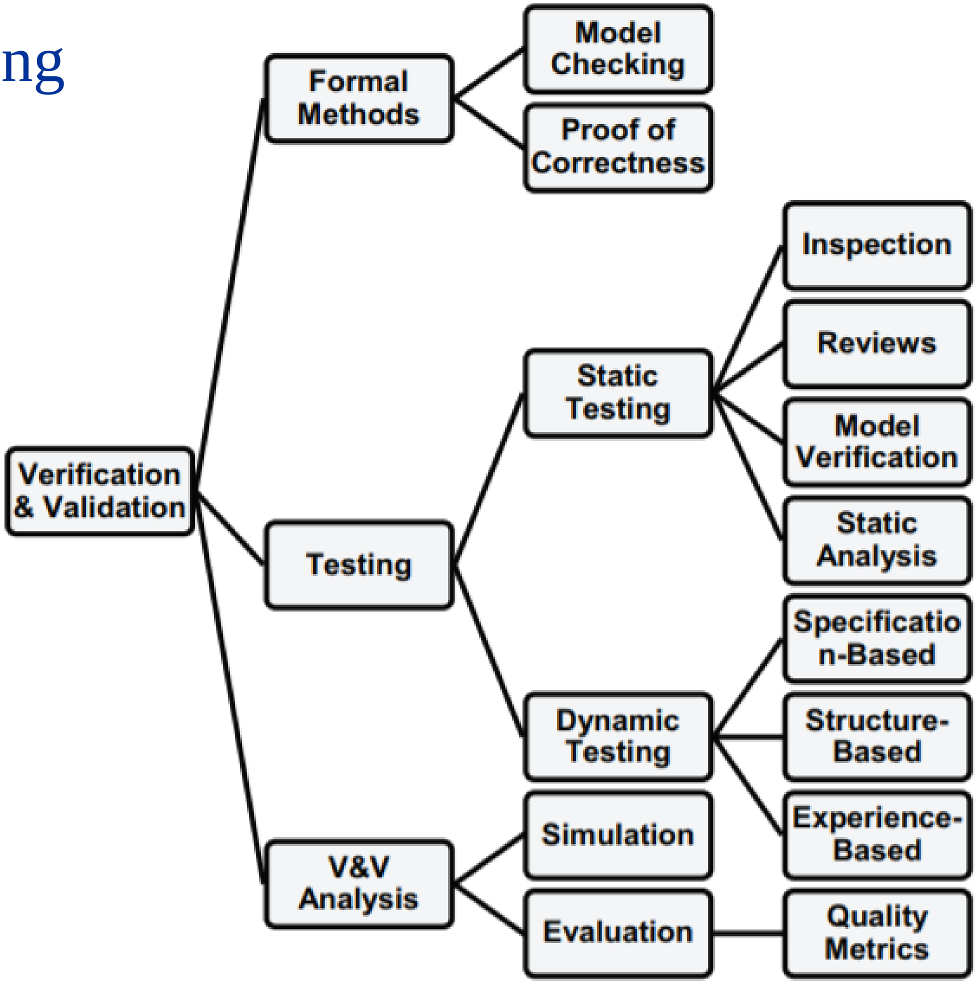
Testing in V&V

- Both verification and validation involves testing
- Verification
  - Whether the code conform with software specification
  - Conformance testing
- Validation
  - Functional testing
  - Scenario testing
  - Risk based testing



Assurance Case

The verification/validation results we have

- Software requirements
- Risk analysis
- Model checking results
- Traceability analysis
- Testing result

Typical risk analysis report

Cause/Fault Tree Ref	Effect/Severity/Likelihood	Mitigation	Verification
Faulty data exchanged among redundant computers causes all computers to fail. This could occur because of Improper requirements, incorrect coding of logic, incorrect data definitions (e.g., initialized data), and/or inability to test all possible modes in the SW	Effect: Loss of operation of system during critical phase, leading to loss of life. Severity: Catastrophic Likelihood: Improbable Class: Controlled	a) Software safeguards reduce, to the maximum extent feasible, the possibility that faulty data sent among redundant computers causes them to fail b) Program Development Specifications and Functional SW Requirements c) Subsystem design and functional interface requirements are used in the design and development of the relevant SW	Extensive validation and testing are in place to minimize generic SW problems. The contractors must perform rigorous reviews throughout the SW definition, implementation, and verification cycles. These review processes cover requirements, design, code, test procedures and results, and are designed to eliminate errors early in the SW life cycle.

Typical risk analysis report

Cause/Fault Tree Ref	Effect/Severity/Likelihood	Mitigation	Verification
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Problems

- Ambiguities makes certification difficult
- Mitigation and verification actions are implicitly related to the causes
- The answers maybe somewhere but difficult to find
- Solution: make the relationships explicit

What is assurance case?

- A justified measure of confidence that a system will function as intended in its environment of use
- Measure of confidence
  - What level of confidence do we have as a result of various assurance activities?
- Justified
  - Why should we have a particular level of confidence?
  - What evidence is there to support this level of confidence?
  - Why do we believe the evidence?
- Function as intended
  - “as intended” by the system’ s users as they are actually using it
  - Minimize impact of unusual (or unexpected) operational conditions
  - Minimize impact of vulnerabilities that can be exploited by hostile entities
- Environment of use
  - Not just the intended environment of use — the actual environment of use

Clarifications

- What assurance case is
  - Improves visual comprehension of existing arguments
  - Improves discussion and reduces time-to-agreement on what evidence is needed and what the evidence means (Having identified argument structure up front)
  - Recognition and exploitation of successful (convincing) arguments becomes possible (assurance case patterns)
  - Supports monitoring of project progress towards successful certification When problems arise it helps with diagnosis
  - When new functionality is added it can quickly pinpoint needed new evidence (and identify existing evidence that need not be reconsidered)

- What assurance case is NOT
  - A verified proof that a product is safe

Types of Assurance cases

- Safety assurance
  - Standard-based
    - Evaluate developer competence based on conformance to process standards
    - Adherence to good development processes is evidence of ability to produce good products
    - Pros: widely accepted, standardized
    - Cons: not suitable for new products with few practitioners
  - Product-based
    - Developers create an assurance case; independent assessors evaluate it.
    - Pros: agilely applicable to areas like aerospace, railways, nuclear power plants, off-shore oil, defense, medical devices, etc.
    - Cons: case by case study
- Confidence assurance
  - For tool developers

Goal Structuring Notation (GSN)

- Developed to help organize and structure Safety Cases in a readily reviewable form

To show how **claims/goals** ▭ are broken down into sub-claims/goals,

and eventually supported by **evidence** ○

while making clear the argumentation **strategies** ▱ adopted,

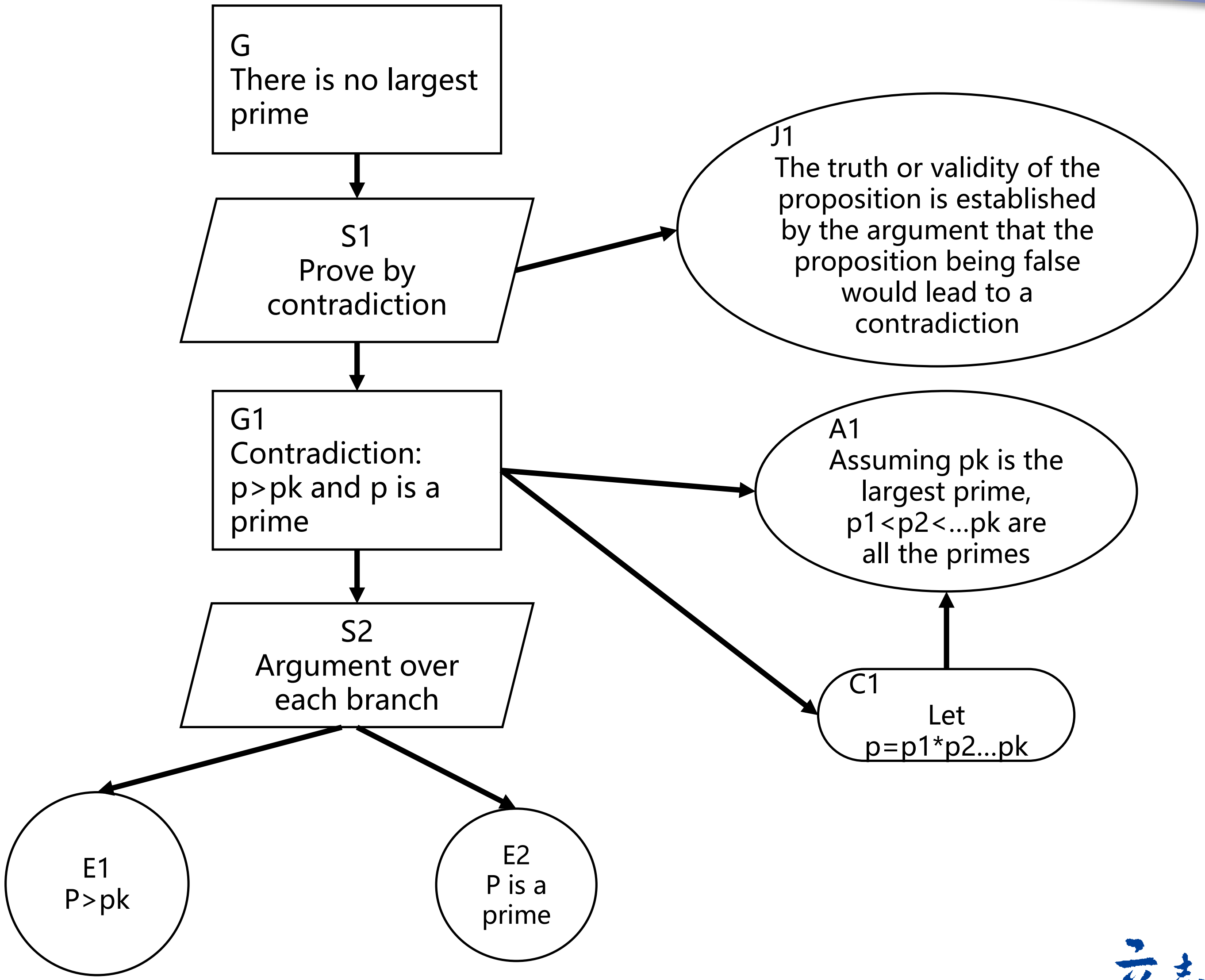
the rationale for the approach (**assumptions, justifications**) ⬭ A/J

and the **context** in which claims are stated ⬭

Example

- Proposition
  - There is no largest prime number.
- Proof
  - Prove by contradiction
  - Assuming there is a largest prime
  - p1<p2<…<pk are all the primes
  - Let p=p1* p2* … * pk+ 1
  - p is not divisible by any prime
  - So p is a prime, larger than pk—a contradiction

GSN argument



G
There is no largest prime

S1
Prove by contradiction

J1
The truth or validity of the proposition is established by the argument that the proposition being false would lead to a contradiction

G1
Contradiction: p>pk and p is a prime

A1
Assuming pk is the largest prime, p1<p2<...pk are all the primes

C1
Let p=p1*p2...pk

S2
Argument over each branch

E1
P>pk

E2
P is a prime

How to construct assurance case

Suggested approach

- The GSN Six-Step Approach
  1. Identify Goals
  2. Define Basis for Goals
  3. Identify Strategies
  4. Define Basis for Strategies
  5. Elaborate Strategies
  6. Identify Basic Solutions/Evidence

- Notes
  - There are other valid suggestive approaches
  - A research topic

Step 1—Identify Goals - Phrasing

- Should be propositions (statements that can be true or false).
  - Noun-Phrase + Verb-Phrase
  - Noun-Phrase
    - System development – the design method, coding, requirements activities, etc.
    - System design – physical & functional properties of design
    - System operation and maintenance – procedures, roles, etc.
    - Testing, Safety and Hazard Analyses – e.g. fault trees, test results
    - Example
      - “Module XYZ123”， “Fault Tree for Top Event Y”，
      - “Testing Activity Z”
  - Verb-Phrases
    - Predicates over the subjects (qualification)

Step 1—Identify Goals - Phrasing

- In an appropriate tense for the intended time of reading.
  - Past tense for development: “System was written in SPARK-ADA subset.”
  - Present tense for system attributes: “Likelihood of Hazard X is 10^{-6}.”
  - Future tense for operation/maintenance: “Maintenance will be carried out every 30 days.”
- Should be positive statements of objectives achieved, not requirements
  - “Failure rate is less than 10^{-6}.” v.s. “Failure rate must be less than 10^{-6}.”
- Difficult to summarize?
  - Use references. i.e. “Requirement 6.3 (A-V Synchrony) has been met”

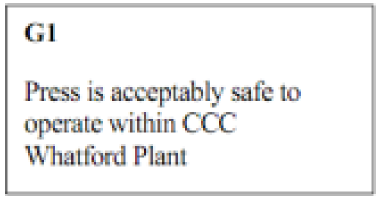
Step 1—Identify Goals - Examples

Subject <Noun-Phrase>	Predicate <Verb Phrase>
Component X	has no critical failure rates
All identified hazards for System Y	have been sufficiently mitigated
Non-destructive examination of weld-site Z	has been performed
Design A	employs triple modular redundancy

Wrong examples:

Claim:	Reason:
“Hazard Log for System Y”	Noun Phrase — describes an entity— not a statement
“Fault Tree for Hazard H-1”	As above
“Perform Fault Tree Analysis of Hazard H-1”	Verb Phrase — an action — not a statement
“How many failure modes does component X have?”	Question — not a statement

Step 1—Identify Goals - Examples



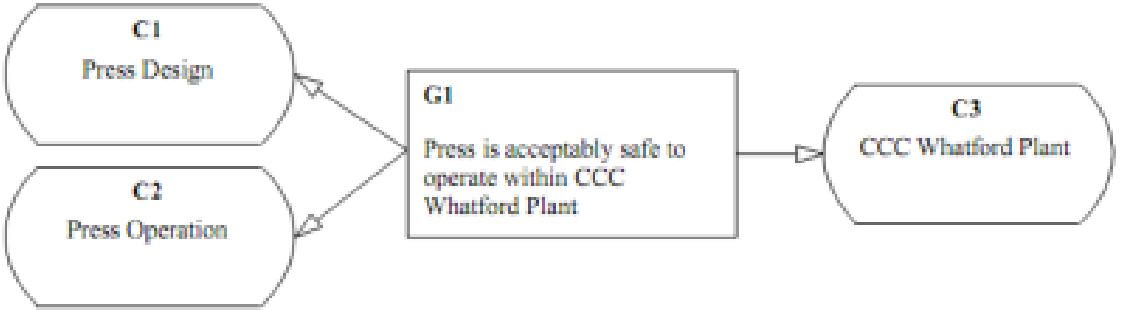
G1

Press is acceptably safe to operate within CCC Whatford Plant

Step 2 – Define basis for claims: Context

- Having presented a claim, make clear (unambiguous) the basis on which that claim is stated
    - When a claim talks of hazards, components, requirements, fault trees, acceptability, sufficiency … is it clear what is being referred to?
- Claims are rarely objective 'context-free' statements (especially when terms such as tolerable and negligible are used)
- The aim is to ensure that both writer and reader have same understanding
- Not helpful: "Requirement 6.3 has been met"
- Three Key Aspects
    - Information about the system under discussion
    - Information about the operation environment for the system
    - Information about the argument (terminology definition, etc.)

Step 2 – Define basis for claims: Context


C1
Press Design
C2
Press Operation
G1
Press is acceptably safe to operate within CCC Whatford Plant
C3
CCC Whatford Plant

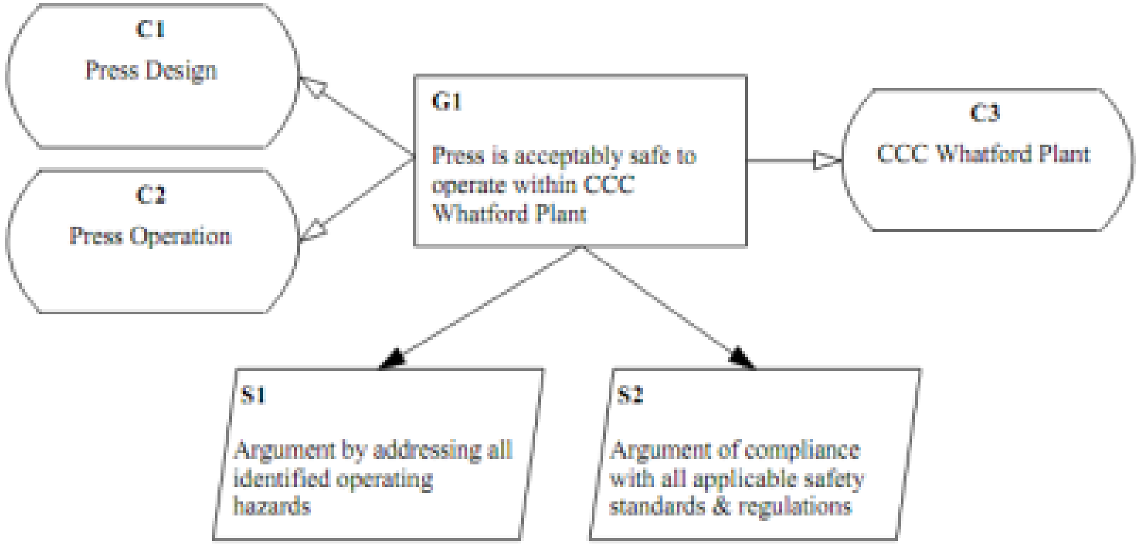
Step 3—Identify Strategies

- Q: When is it necessary to explicitly introduce a strategy node?
  - A1: Whenever you wish to explain the relationship between a claim and its sub-claims
    - Ask yourself whether the reader will understand how you have broken down the claim into sub-claims
  - A2: Whenever the strategy requires additional (contextual) information, justification or assumptions

Step 3—Identify Strategies - phrasing

- Strategies should not be imperative verb-phrases
  - e.g. “Use Historical Data”
- Strategies should be expressed from the perspective of the argument approach, not the design, testing, or analysis approach
  - e.g., “Argument by appeal to interlock” rather than “Interlocks used”
- Strategies should not contain claims
  - Should be possible to remove strategy nodes and not affect the argument being made

Step 3—Identify Strategies

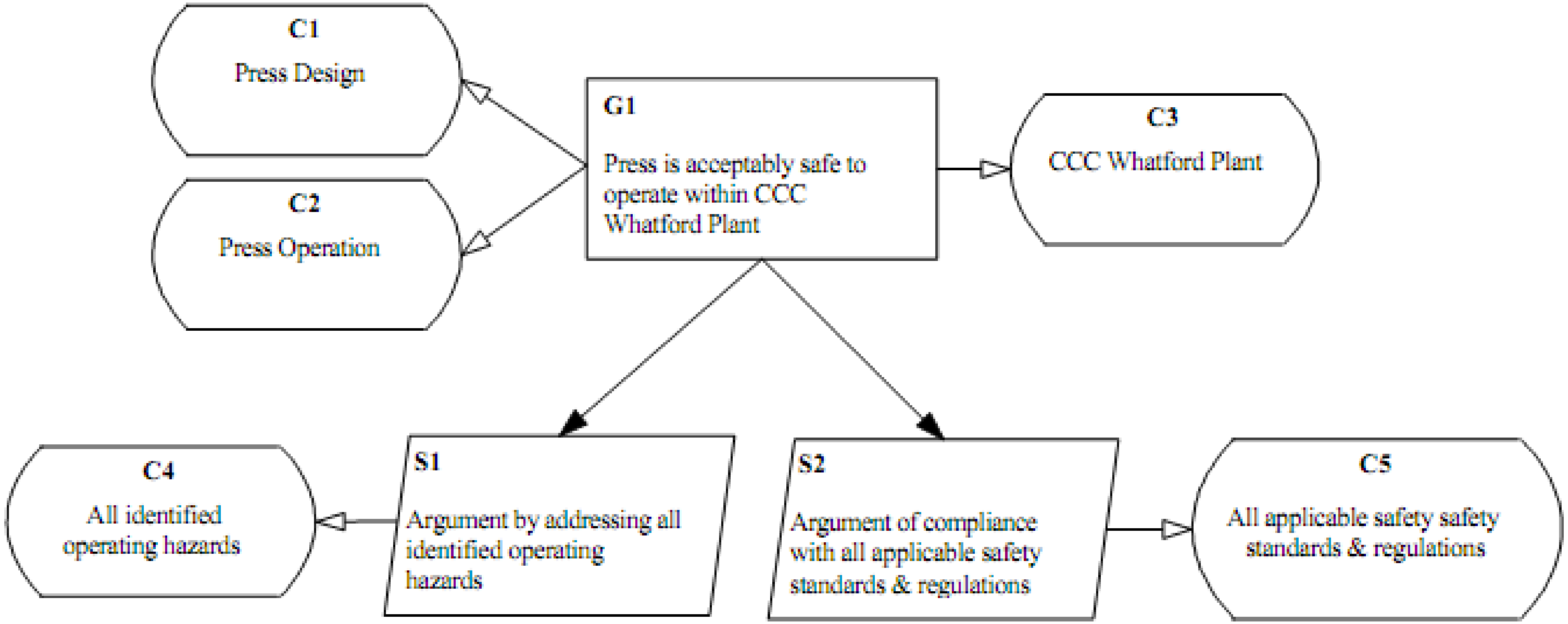


C1
Press Design
C2
Press Operation
G1
Press is acceptably safe to operate within CCC Whatford Plant
C3
CCC Whatford Plant
S1
Argument by addressing all identified operating hazards
S2
Argument of compliance with all applicable safety standards & regulations

Step 4 – Define basis for strategy

- Contexts
  - Similar to contexts for goals, providing necessary contextual information (models, definitions, etc.)
- Rationales
  - Assumptions
    - Are there any assumptions on which the strategy/goal is being put forward as a solution to the parent goal?
  - Justifications
    - Why that particular strategy/goal is being put forward as a solution to the parent claim?
- Phrasing
  - Both assumptions and justifications are statements and should be expressed as claims.

Step 4 – Define basis for strategy


C1
Press Design

C2
Press Operation

G1
Press is acceptably safe to operate within CCC Whatford Plant

C3
CCC Whatford Plant

C4
All identified operating hazards

S1
Argument by addressing all identified operating hazards

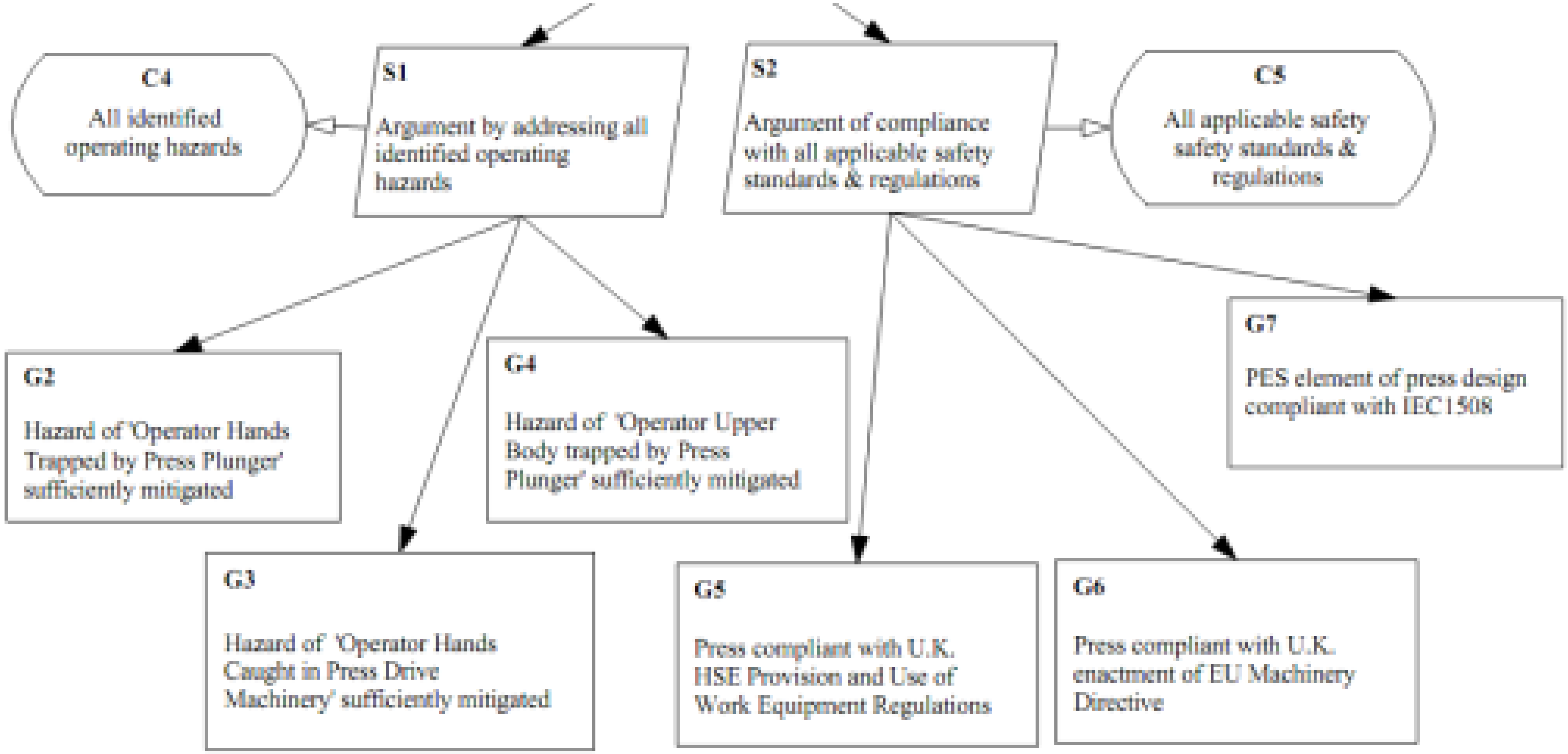
S2
Argument of compliance with all applicable safety standards & regulations

C5
All applicable safety safety standards & regulations

Step 5—Elaborating Strategies

- To develop subgoals/solutions to support strategies
  - Depending on the strategies, different structures may be put forward as goals.
    - E.g., if the strategy is "argument over all system safety properties," then each safety property is a subgoal to put forward.
    - E.g., if the strategy is "argument by quantitative analysis result," then quantitative claims must be put forward.
- Notes
  - Strategies are just a means of clarifying how goals/claims/solutions at different levels are related to one another.

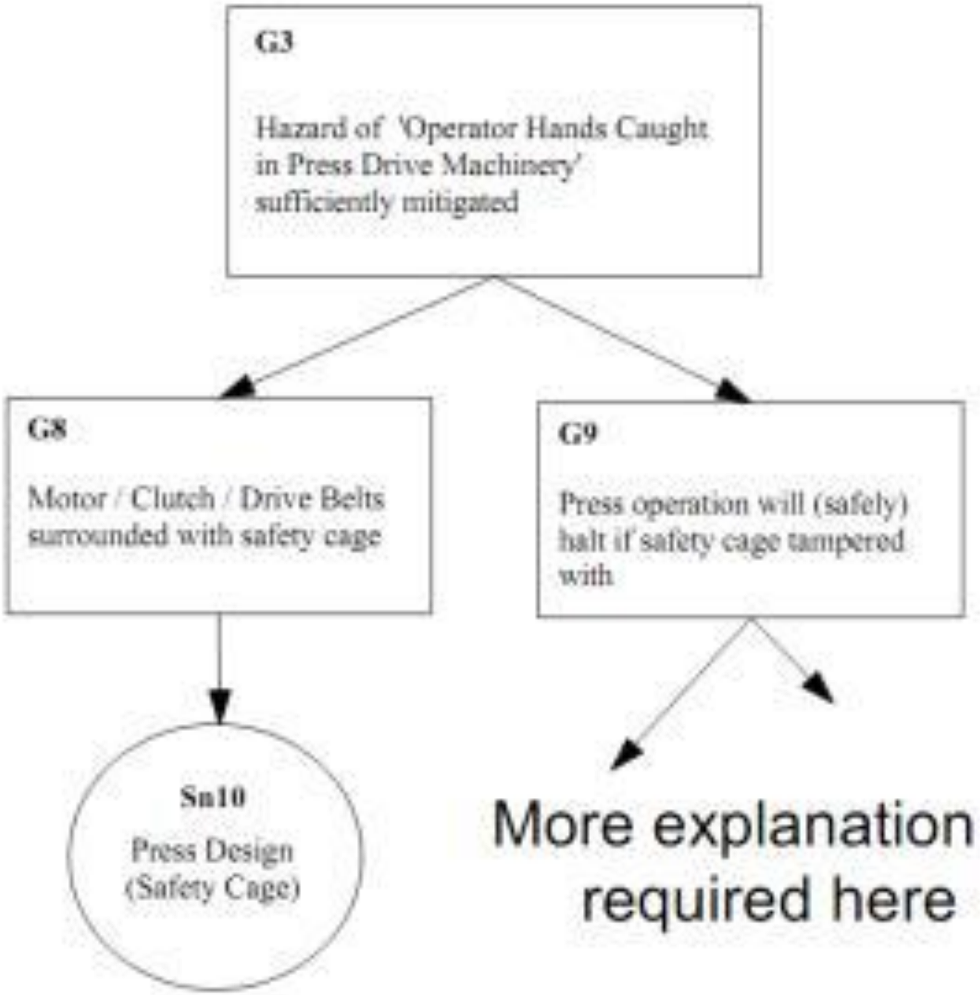
Step 5—Elaborating Strategies


C4
All identified operating hazards
S1
Argument by addressing all identified operating hazards
S2
Argument of compliance with all applicable safety standards & regulations
C5
All applicable safety safety standards & regulations
G2
Hazard of 'Operator Hands Trapped by Press Plunger' sufficiently mitigated
G3
Hazard of 'Operator Hands Caught in Press Drive Machinery' sufficiently mitigated
G4
Hazard of 'Operator Upper Body trapped by Press Plunger' sufficiently mitigated
G5
Press compliant with U.K. HSE Provision and Use of Work Equipment Regulations
G6
Press compliant with U.K. enactment of EU Machinery Directive
G7
PES element of press design compliant with IEC1508

Step 6—Identifying Solutions/evidence

- Solutions/evidence
  - “Leaf goals” that do not need further explanation, expansion, or refinements.
  - Can be supported by direct reference to external evidence.
  - Come from
    - Test results, analysis reports, facts, etc.
- Watchout
  - Jumping to a solution too soon

Step 6—Identifying Solutions



G3

Hazard of 'Operator Hands Caught in Press Drive Machinery' sufficiently mitigated

G8

Motor / Clutch / Drive Belts surrounded with safety cage

G9

Press operation will (safely) halt if safety cage tampered with

Sn10

Press Design (Safety Cage)

More explanation required here

Assurance case recognition by FDA

- 510(k) submissions for infusion pumps are REQUIRED to have an assurance case
- The requirement may extend to all drug delivery devices
- The FDA encourages device manufacturers to submit safety assurance as part of pre-market submissions
- ISO/IEC 15026-2: Systems and software engineering — Systems and software assurance — Part 2: Assurance case

Conclusion

- Pros
  - is a way of organizing assurance arguments structurally.
  - applies mainly in safety-critical domains and for complex systems.
  - is an active research area.
- Cons
  - has limitations in building, reviewing, maintaining, and reusing.
  - has tool support, but not adequate.

References

- Insup Lee, Assurance Cases: An Introduction, University of Pennsylvania
- Charles B. Weinstock, Assurance Cases.Software Engineering Institute, Carnegie Mellon University, December 2008.
- George Cleland and Robin Bloomfield, Assurance Cases for Medical Devices: The ASCE Approach. Adelard LLP. Silver Spring, Maryland, September 28-29, 2010.
- Charles B. Weinstockand John B. Goodenough, Towards an Assurance Case Practice for Medical Devices. Technical Note, CMU/SEI-2009-TN-018.

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

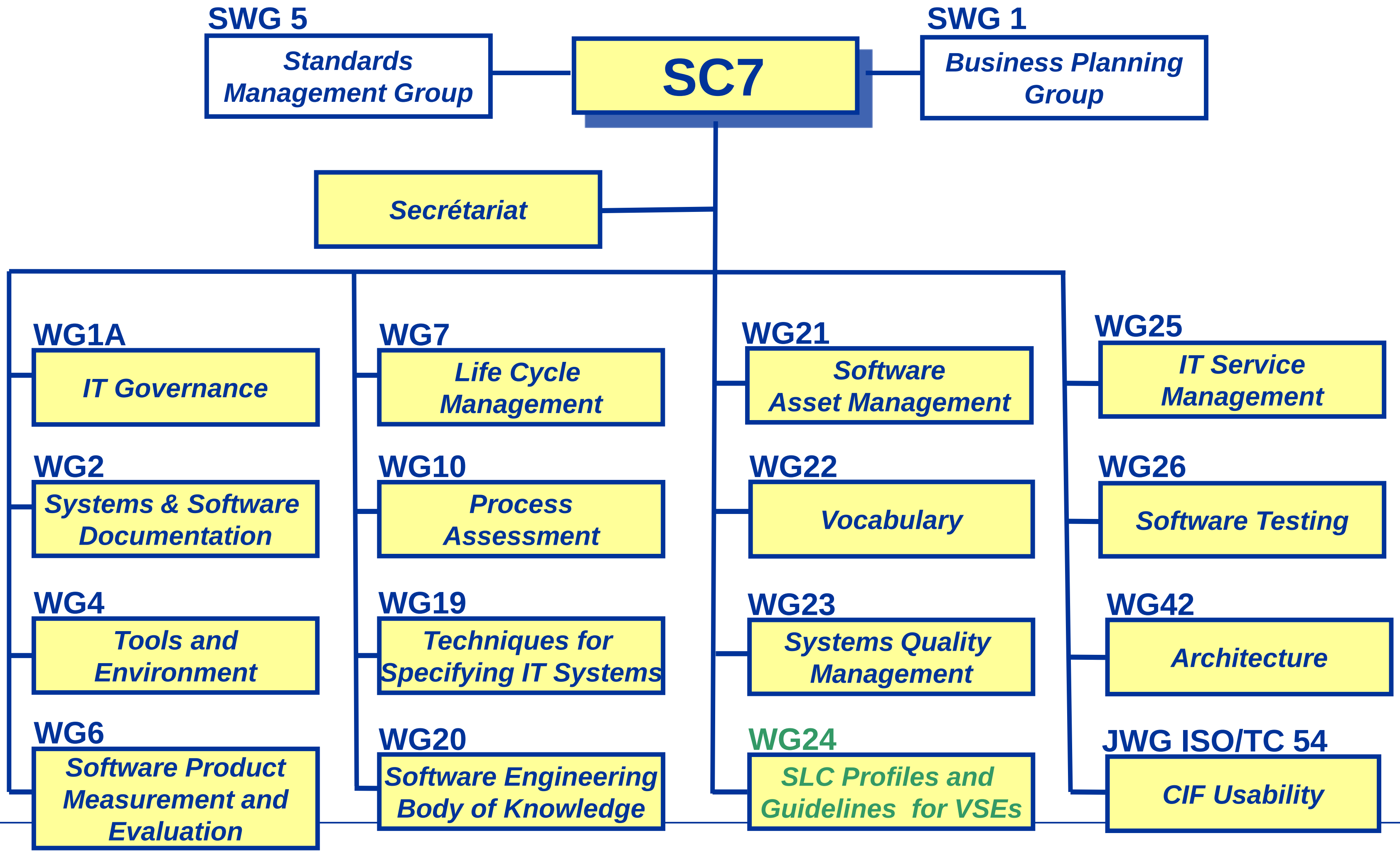
- The resulting document is circulated as a Draft International Standard (DIS) to all ISO's member bodies for voting and comment

- 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

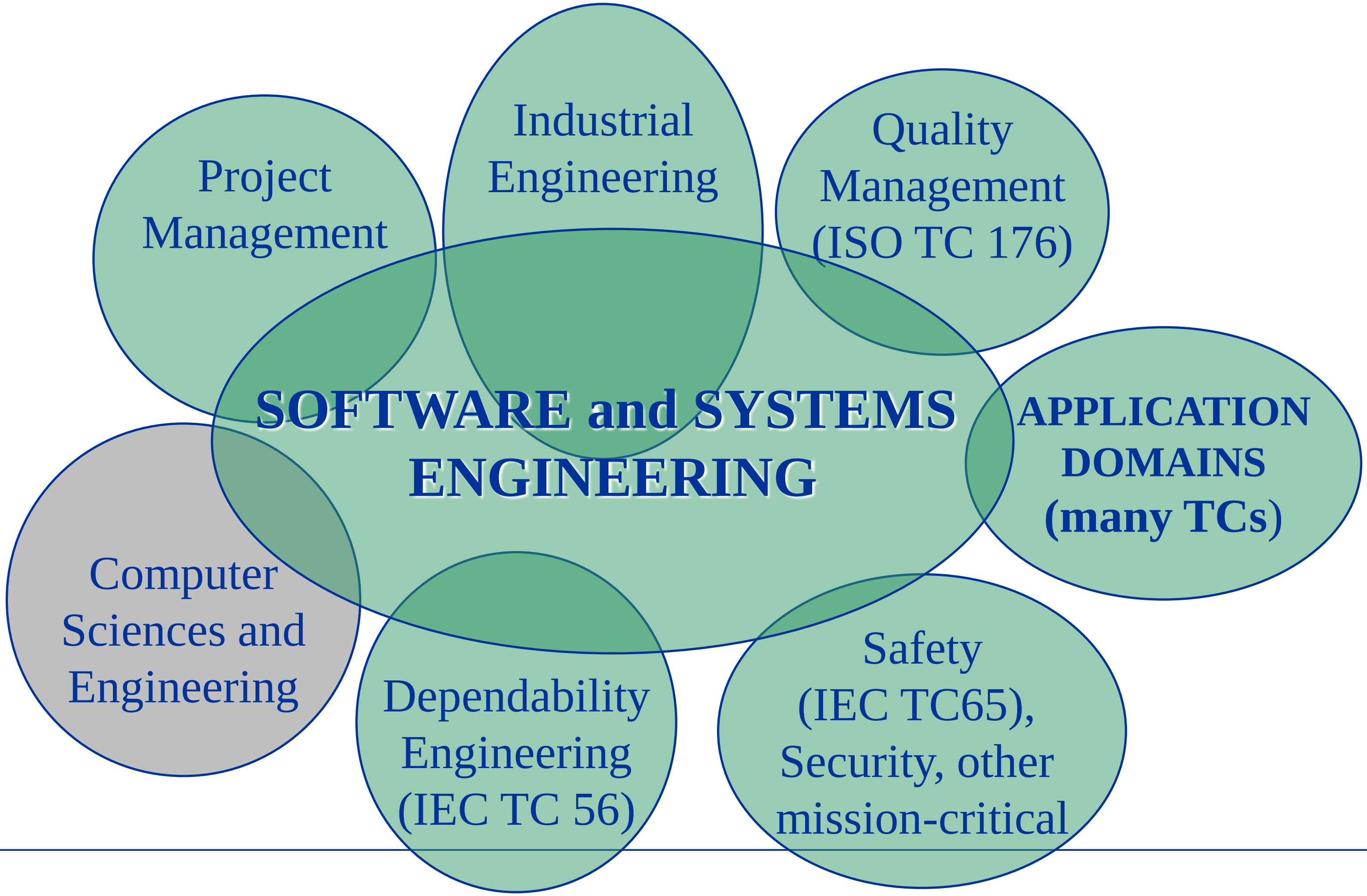
- ISO/IEC JTC 1 SC7
  - International Organization for Standardization/ International Electrotechnical Commission Joint Technical Committee 1 Sub-Committee 7
- ISO/IEC JTC 1 SC7 Terms of Reference
  - “Standardization of processes, methods and supporting technologies for the engineering and management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

SC7 Structure


SWG 5
Standards Management Group
SC7
SWG 1
Business Planning Group
Secrétariat
WG1A
IT Governance
WG2
Systems & Software Documentation
WG4
Tools and Environment
WG6
Software Product Measurement and Evaluation
WG7
Life Cycle Management
WG10
Process Assessment
WG19
Techniques for Specifying IT Systems
WG20
Software Engineering Body of Knowledge
WG21
Software Asset Management
WG22
Vocabulary
WG23
Systems Quality Management
WG24
SLC Profiles and Guidelines for VSEs
WG25
IT Service Management
WG26
Software Testing
WG42
Architecture
JWG ISO/TC 54
CIF Usability

‡ Adapted from Prof. M. Azuma

Domains covered by SC7


Industrial Engineering
Project Management
Quality Management (ISO TC 176)
SOFTWARE and SYSTEMS ENGINEERING
APPLICATION DOMAINS (many TCs)
Computer Sciences and Engineering
Dependability Engineering (IEC TC 56)
Safety (IEC TC65), Security, other mission-critical

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 <u>all medical devices</u> 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.