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Information sharing on Software validation

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4th Joint Conference of Taiwan and Japan on Medical Products Regulation

Tokyo 7 Dec 2016

Brief History of Software

- 2400 BCE Abacus in Babylon
- 1185~1005 BCE Abacus in Zhou Dynasty, China,
- 500 BCE Abacus in Ancient India,
- 1822 First mechanical computer invented by English mathematician Charles Babbage
- 1911 IBM founded from a merger of several companies
- 1939 First digital computer "Atanasoff-Berry Computer"
- 1940 First programmable digital computer "Colossus"
- 1955 Computer Usage Company founded, first to sell software separately from computer hardware/1957 ADP uses IBM mainframe computers to process pay roll
- 1972 SAP founded, first to sell enterprise software/1975 Microsoft founded/1976 Apple I/1977 Oracle developed/1978 first accounting software "Peachtree" /1979 first spreadsheet software "Visicalc"
- 1989 Microsoft Office
- 1991 Linux /1993 first web browser "Mosaic"
- 2000" Dot-Com" bubble burst/2006 Google apps/2007 iPhone/ 2007 rise of big data
- 2010 Rise of tablet computing/ 2012 Rise of wearable technology
- 2016 Intel: "The end of Moore's law" '

Source: 九章數學教育基金會，Wikipedia

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Outline

1. Software in Medical Device Regulation
2. Software Standards and Guidance
3. Software Validation

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Software in Medical Device Regulation

1) Software as medical device
2) QMS software
3) Production and service software
4) Software as result of a process

NOTE:

1. There are other concerns such as electronic signature and clinical trial management system.
2. For electronic signature, refer to law/regulation of each jurisdiction such as 電子簽章法(Electronic Signatures Act) of R.O.C. or 電子署名及び認証業務に関する法律 of Japan
3. For clinical trial management system, refer to US FDA guidance Computerized Systems Used in Clinical Investigations, 2007.

1) Software as a Medical Device

- **ISO 13485: 2016 3.11 medical device**

  instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, **software**, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purpose(s) of:

  — diagnosis, prevention, monitoring, treatment or alleviation of disease;

  — diagnosis, monitoring, treatment, alleviation of or compensation for an injury;

  — investigation, replacement, modification, or support of the anatomy or of a physiological process;

  — supporting or sustaining life;

  — control of conception;

  — disinfection of medical devices;

  — providing information by means of in vitro examination of specimens derived from the human body;

1) Software as a Medical Device

- **IMDRF/SaMDWG/N10FINAL:2013 Software as a Medical Device (SaMD): Key Definitions 5.1 Software as a Medical Device**

  The term "Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

1) Software as a Medical Device

- **IMDRF/SaMDWG/N10FINAL:2013 Software as a Medical Device (SaMD): Key Definitions 5.1 Software as a Medical Device**

  NOTES

  - SaMD is a medical device and includes in-vitro diagnostic (IVD) medical device.
  - SaMD is capable of running on general purpose (non-medical purpose) computing platforms
  - "without being part of" means software not necessary for a hardware medical device to achieve its intended medical purpose;
  - Software does not meet the definition of SaMD if its intended purpose is to drive a hardware medical device
  - SaMD may be used in combination (e.g., as a module) with other products including medical devices;
  - SaMD may be interfaced with other medical devices, including hardware medical devices and
  - other SaMD software, as well as general purpose software
  - Mobile apps that meet the definition above are considered SaMD

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Medical Device Software

- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, 2005, Scope
  - For the purposes of this document, we refer to devices that contain one or more software components, parts, or accessories, or are composed solely of software as "software devices," including:
    - firmware and other means for software-based control of medical devices
    - stand-alone software applications
    - software intended for installation in general-purpose computers
    - dedicated hardware/software medical devices.
    - accessories to medical devices when those accessories contain or are composed of software
- IEC 62304:2006 Medical device software—Software life cycle processes, Scope (1.2 Filed of application)
  - software is itself a medical device
  - software is an embedded or integral part of the final medical device

1) Software as a Medical Device

- **Article 13 Pharmaceutical Affairs Act (R.O.C.)**

  The term "medical device", as used in this Act, shall refer to any instruments, machines, apparatus, materials, **software**, reagent for in vitro use, and other similar or related articles, which is used in diagnosing, curing, alleviating, or directly preventing human diseases, regulating fertility, or which may affect the body structure or functions of human beings, and do not achieve its primary intended function by pharmacological, immunological or metabolic means in or on the human body.

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2) QMS Software

ISO 13485: 2016 4.1.6

The organization shall document procedures for the validation of the application of computer software used in the quality management system. Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application.

The specific approach and activities associated with software validation and revalidation shall be proportionate to the risk associated with the use of the software.

Records of such activities shall be maintained (see 4.2.5).

3) Production and Service Software

ISO 13485: 2016 6.3 Infrastructure

The organization shall document the requirements for the infrastructure needed to achieve conformity to product requirements, prevent product mix-up and ensure orderly handling of product.

Infrastructure includes, as appropriate:

a) buildings, workspace and associated utilities;

b) process equipment (both hardware and software);

c) supporting services (such as transport, communication, or information systems).

The organization shall document requirements for the maintenance activities, including the interval of performing the maintenance activities, when such maintenance activities, or lack thereof, can affect product quality. As appropriate, the requirements shall apply to equipment used in production, the control of the work environment and monitoring and measurement.

Records of such maintenance shall be maintained (see 4.2.5).

3) Production and Service Software

ISO 13485: 2016 7.5.6 Validation of processes for production and service provision

The organization shall validate any processes for production and service provision where the resulting output cannot be or is not verified by subsequent monitoring or measurement and, as a consequence, deficiencies become apparent only after the product is in use or the service has been delivered.

…

The organization shall document procedures for the validation of the application of **computer software used in production and service provision**. Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application. The specific approach and activities associated with **software validation** and revalidation shall be proportionate to the risk associated with the use of the software, including the effect on the ability of the product to conform to specifications.

Records of the results and conclusion of validation and necessary actions from the validation shall be maintained (see 4.2.4 and 4.2.5).

3) Production and Service Software

ISO 13485: 2016 7.6 Control of monitoring and measuring equipment

…

The organization shall document procedures for the validation of the application of computer software used for the monitoring and measurement of requirements. Such software applications shall be validated prior to initial use and, as appropriate, after changes to such software or its application.

The specific approach and activities associated with software validation and revalidation shall be proportionate to the risk associated with the use of the software, including the effect on the ability of the product to conform to specifications.

Records of the results and conclusion of validation and necessary actions from the validation shall be maintained (see 4.2.4 and 4.2.5).

4) Software as Result of a Process

ISO 13485: 2016 3.15 product: result of a process

Note 1 to entry: There are four generic product categories, as follows:

— services (e.g. transport);

— software (e.g. computer program, dictionary);

— hardware (e.g. engine mechanical part);

— processed materials (e.g. lubricant).

Many products comprise elements belonging to different generic product categories. Whether the product is then called service, software, hardware or processed material depends on the dominant element. For example, the offered product "automobile" consists of hardware (e.g. tyres), processed materials (e.g. fuel, cooling liquid), software (e.g. engine control software, driver's manual), and service (e.g. operating explanations given by the salesman).

Software consists of information and is generally intangible and can be in the form of approaches, transactions or procedures.

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Medical Device Software Concerns

- Software verification, validation and testing: life cycle process
- Software risk management
- Medical mobile apps
- Wireless
- Cybersecurity
- Interoperability

Medical Device Software Related Standards

Topics	Software Related Standards
Software life cycle processes	IEC 62304:2006+AMD1:2015 Medical device software - Software life cycle processes
	AAMI TIR 45:2012 Guidance on the Use of AGILE Practices in the Development of Medical Device Software
	AAMI ANSI SW87:2012 Application of Quality Management System Concepts to Medical Device Data Systems
Risk Management	IEC 80001-1 Edition 1.0 2010-10 Application of Risk Management for IT - Networks Incorporating Medical Devices - Part 1: Roles, Responsibilities and Activities
	IEC/TR 80002-1: 2009 Medical Device Software - Part 1: Guidance on the Application of ISO 14971 to Medical Device Software
	IEC 80001-2-1 Edition 1.0 2012-07 Application of Risk Management for IT- Networks Incorporating Medical Devices - Part 2-1: Step-By-Step Risk Management of Medical IT-Networks - Practical Applications And Examples
	IEC 80001-2-4 Edition 1.0 2012-11 Application of Risk Management for IT-Networks Incorporating Medical Devices -- Part 2-4: Application Guidance - General Implementation Guidance for Healthcare Delivery Organization
	IEC TR 80001-2-2 Edition 1.0 2012-07 Application of Risk Management for IT Networks Incorporating Medical Devices - Part 2-2: Guidance for the Disclosure and Communication of Medical Device Security Needs, Risks and Controls
	IEC TR 80001-2-3 Edition 1.0 2012-07 Application of Risk Management for IT Networks Incorporating Medical Devices - Part 2-3: Guidance for Wireless Networks
	IEC TR 80001-2-5 2014 Application of Risk Management for IT-Networks Incorporating Medical Devices Part 2-5: Application Guidance-- Guidance for Distributed Alarm Systems
Cybersecurity	IEC 62443-2-1: 2010 Industrial Communication Networks - Network And System Security - Part 2-1: Establishing an Industrial Automation And Control System Security Program
	IEC/TS 62443-1-1:2009 Industrial Communication Networks - Network And System Security - Part 1-1: Terminology, Concepts and Models
	IEC/TR 62443-3-1:2009 Industrial Communication Networks - Network And System Security - Part 3-1: Security Technologies For Industrial Automation And Control Systems
	ISO 29147:2014 Information Technology - Security Techniques - Vulnerability Disclosure
	ISO 30111:2013 Information Technology - Security Techniques - Vulnerability Handling Processes
Interoperability	ISO/IEEE 11073 Health informatics - Medical / health device communication standards

US FDA
Medical Device Software Validation Related Guidance

Topics	Guidance	Date
General Wellness	General Wellness: Policy for Low Risk Devices - Draft Guidance for Industry and Food and Drug Administration Staff	2015.01.20
Mobile Apps	Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff	2015.02.09
Software Validation and Premarket Submission	General Principles of Software Validation	2002.01.11
	Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices	2005.05.11
Wireless Technology	Guidance for Industry - Wireless Medical Telemetry Risks and Recommendations	2000.09.27
	Deciding When To Submit A 510(k) For A Change To An Existing Wireless Telemetry Medical Device: Final Guidance for FDA Reviewers and Industry	2000.11.30
	Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff	2013.08.14
Cybersecurity	Information for Healthcare Organizations about FDA's Guidance for Industry: Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software	2005.0209
	Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software- Guidance for Industry	2005.01.14
	Content of Premarket Submissions for Management of Cybersecurity in Medical Devices - Guidance for Industry and Food and Drug Administration Staff	2014.10.02
	Postmarket Management of Cybersecurity in Medical Devices- Draft Guidance for Industry and Food and Drug Administration Staff	2016.1.22
Interoperability	Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices- Draft Guidance for Industry and Food and Drug Administration Staff	2016.1.26

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Software Validation

- The Quality System regulation is harmonized with ISO 8402:1994, which treats **"verification" and "validation" as separate and distinct terms**. On the other hand, many software engineering journal articles and textbooks use the terms **"verification" and "validation" interchangeably**, or in some cases refer to software "**verification, validation, and testing (VV&T)**" as if it is a single concept, with no distinction among the three terms.
- Software verification provides objective evidence that the design outputs of a particular phase of the software development life cycle meet all of the specified requirements for that phase. Software verification looks for consistency, completeness, and correctness of the software and its supporting documentation, as it is being developed, and provides support for a subsequent conclusion that software is validated. Software testing is one of many verification activities intended to confirm that software development output meets its input requirements. Other verification activities include various static and dynamic analyses, code and document inspections, walkthroughs, and other techniques.

Source: 3.1.2 Verification and Validation, General Principles of Software Validation;, 2002 , US FDA

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Software Validation

- **Software validation is a part of the design validation** for a finished device, but is not separately defined in the Quality System regulation. For purposes of this guidance, FDA considers software validation to be "confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled." In practice, software validation activities may occur both during, as well as at the end of the software development life cycle to ensure that all requirements have been fulfilled. Since software is usually part of a larger hardware system, the validation of software typically includes evidence that all software requirements have been implemented correctly and completely and are traceable to system requirements. A conclusion that software is validated is highly dependent upon comprehensive software testing, inspections, analyses, and other verification tasks performed at each stage of the software development life cycle. Testing of device software functionality in a simulated use environment, and user site testing are typically included as components of an overall design validation program for a software automated device.

Source: 3.1.2 Verification and Validation, General Principles of Software Validation;, 2002, USFDA

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Software Validation

- **Software verification and validation are difficult** because a developer cannot test forever, and it is hard to know how much evidence is enough. In large measure, software validation is a matter of developing a "level of confidence" that the device meets all requirements and user expectations for the software automated functions and features of the device. Measures such as defects found in specifications documents, estimates of defects remaining, testing coverage, and other techniques are all used to develop an acceptable level of confidence before shipping the product. The level of confidence, and therefore the level of software validation, verification, and testing effort needed, will vary depending upon the safety risk (hazard) posed by the automated functions of the device.

Source: 3.1.2 Verification and Validation, General Principles of Software Validation;, 2002, US FDA

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Reasons for recalls (US FDA, FY 2010 – FY 2012)

Reasons for recalls	Number
Nonconforming Material/Component	429
Software Design(Device)	429
Device Design	425
Process Control	266
Component Design/Selection	144
Employee Error	134
Labeling Mixups/Errors	99
Under Investigation by the Firm	81
Process Design	77
Packaging Process Control	76
Error In Labeling	59
Packaging	58
Mix-up of Material/Components	49
Material/Component Contamination	47
Labeling Design	42
Radiation Control for Health and Safety Act	41
Labeling False And Misleading	39
Component Change Control	37

Reasons for recalls	Number
Equipment Maintenance	31
Process Change Control	31
Software Change Control	24
Software Design (Process)	22
PMA- Illegally Marketed	21
Labeling Change Control	19
Packaging Design/Selection	18
Release of Material/Component Prior to Receiving Test results	15
Expiration Dating	15
Vendor Change Control	12
Packaging Change Control	8
Manufacturing Material Removal	8
Storage	7
Environmental Control	6
Unknown/Undetermined by the Firm	6
Finished Device Change Control	4
Reprocessing Controls	2

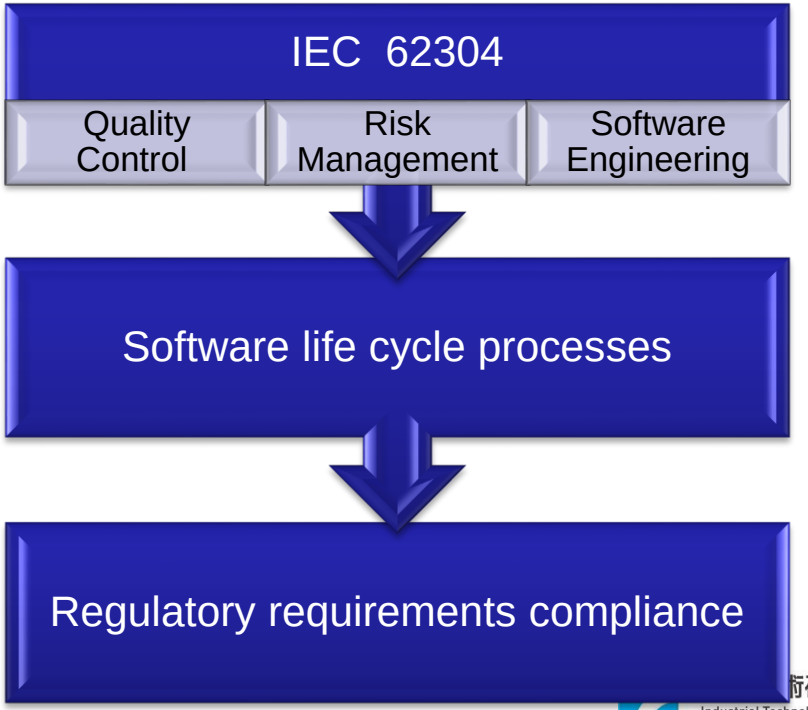
Source : (US FDA) Medical Device Recall Report FY2003 to FY2012

IEC 62304: 2006 Medical device software – Software life cycle processes

ROC	US	EU	Japan	China
IEC 62304:2006 Medical device software—Software life cycle processes	IEC 62304:2006 +AMD1:2015 Medical device software—Software life cycle processes	EN/IEC 62304:2006/AC:2008 Medical device software—Software life cycle processes EN 62304 Q&A Guidance (2013)	JIS T 2304:2012 Medical device software—Software life cycle processes	YY/T 0664-2008醫療器械軟體-軟體生存週期過程(IEC 62304)

- IEC 62304 is based on
  - ISO/IEC 12207:1995, Information Technology –Software Life Cycle Processes
  - ANSI/AAMI/SW 68:2001, Medical Device Software – Software Life Cycle Processes (superseded std.)
- IEC 62304
  - Safety classification added. (3 classes with specific tasks for each).

IEC 62304:2006+AMD1:2015 updates
- Legacy software
- Software safety classification with a risk-based approach



IEC 62304: 2006 Medical device software – Software life cycle processes

4. General requirements

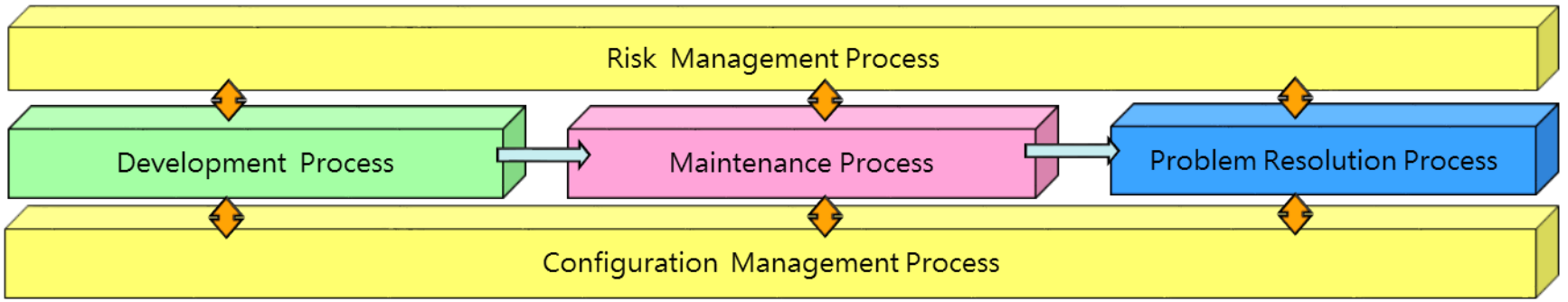
5. Software development process

6. Software maintenance process

7. Software risk management process

8. Software configuration process

9. Software problem resolution process



Source: IEC 62304:2006+AMD1:2015Medical device software - Software life cycle processes

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IEC 62304: 2006 Medical device software – Software life cycle processes

General requirements

- QMS
- Risk management
- Software safety classification

Software development process

- Planning
- Requirements analysis
- Architectural design
- Detailed design
- Unit implementation and verification
- Integration and integration testing
- System testing, release

Source: IEC 62304:2006+AMD1:2015Medical device software - Software life cycle processes

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IEC 62304: 2006 Medical device software – Software life cycle processes

Software maintenance process	• Maintenance plan • Problem and modification analysis • Modification implementation
Software risk management process	• Analysis of software contributing to hazardous situations • Risk control measures • Verification of risk control measures • Risk management of software changes

Source: IEC 62304:2006+AMD1:2015Medical device software - Software life cycle processes

IEC 62304: 2006 Medical device software – Software life cycle processes

Software configuration process	• Configuration identification • Change control • Configuration status accounting
Software problem resolution process	• Problem reports • Investigate the problem • Advise relevant parties • Use change control process • Maintain records • Analyse problems for trends • Verify software problem resolution • Test documentation contents

Source: IEC 62304:2006+AMD1:2015Medical device software - Software life cycle processes

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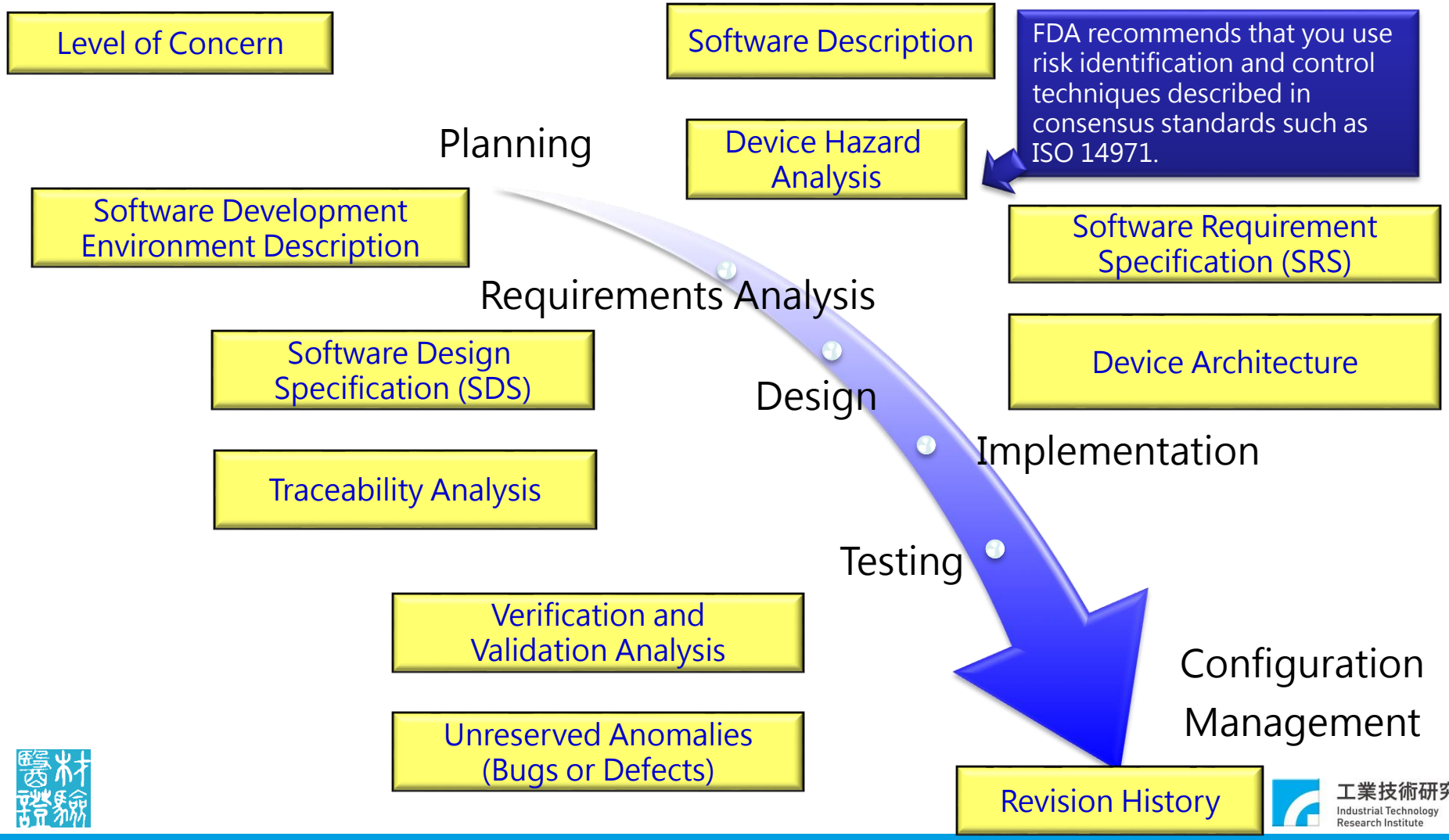
US FDA
Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, 2005



IEC 62304 Safety Classification vs. FDA Level of Concern

IEC 62304 Software Safety Classification	FDA Pre-market Submission Software Levels of Concern
Class A: No injury or damage to health is possible	Minor: failure or latent design flaws are unlikely to cause any injury
Class B: Non-serious injury is possible	Moderate: failure or latent possible design flaw could directly or indirectly result in minor injury
Class C: Death of Serious injury is possible	Major: failure or flaw could directly or indirectly result in death or serious injury

Software in Medical Device Regulation

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- ***No specific standard or guidance for the validation of software used in medical device QMS***
- ***AAMI TIR36:2007, Validation of Software for Regulated Processes provides tool box and examples.***

NOTE: For pharmaceutical industry:

- 電腦化系統確效指導手冊, Taiwan Food and Drug Administration, 2002
- EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines Annex 11 Computerised Systems
- US FDA Guidance for Industry Process Validation: General Principles and Practices 2011
- WHO Supplementary Training Modules: Validation, Water, Air Handling Systems Validation (Part 5): Computerized system validation
- GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems, ISPE

Considerations on Validation of Non-Medical Device Software

- Determine whether the software
  - Is developed by the manufacturer
  - Is developed by sub-contracted software developer
  - Is developed by the manufacturer based on off-the-shelf software
  - Is purchased business software package
  - Should be validated independently or with hardware equipment

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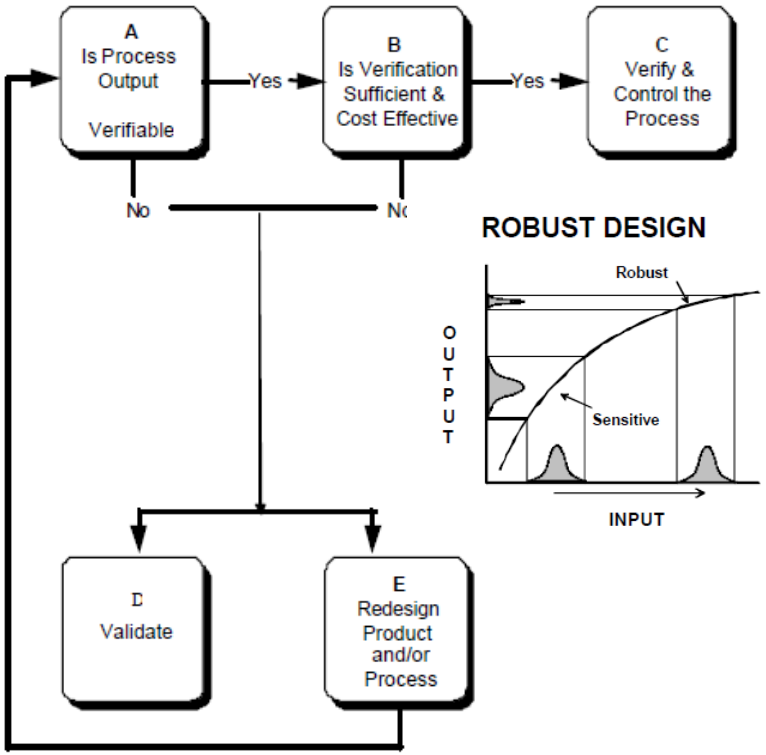
Validation of SW/HW Equipment

This guideline applies to processes which are controlled by computers, but does not cover software validation.

1) Form multi-functional team for validation
2) Plan the approach and define the requirements
3) Identify and describe the processes
4) Specify process parameters and desired output
5) Decide on verification and/or validation
6) Create a master validation plan
7) Select methods and tools for validation
8) Create validation protocols
9) Perform IQ, OQ, PQ and document results
10) Determine continuous process controls
11) Control the process continuously



Process validation decision tree

Source: GHTF/SG3/N99 - 10:2004 (Edition 2)

Validation of SW/HW Equipment

2.1 Installation qualification (IQ): establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’ s approved specification and that the recommendations of the supplier of the equipment are suitably considered.

2.2 Operational qualification (OQ): establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

2.3 Performance qualification (PQ): establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

2.4 Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

2.5 Process validation protocol: a document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

2.6 Verification: confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

Source: GHTF/SG3/N99 - 10:2004 (Edition 2)

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ご清聴ありがとうございました
謝謝聆聽，敬請指教

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