GMP Revised!

Main thrust of the QSR (Quality System Regulation)

- *FDA Mission: Safe and Effective Medical Devices*
- *Medical Device Manufacturing must be conducted in a STATE OF CONTROL.*
- *Control may be achieved by having WRITTEN procedures, and by TRAINING, usually BOTH.*
- *Control requires monitoring of compliance to procedures, AUDITING.*

Design Controls: Seminar Objectives-

- *Provide a working understanding of FDA requirements for design controls.*
- *Instill the skills to devise and implement an FDA compliant design control system in your company.*
- *Provide tools which will result in safer product designs and smoother regulatory submissions processes.*

Today's topics:

- *Introduction - Historical..*
- *Requirements Overview..*
- *Design and Development Planning*
- *Design Input*
- *Design Reviews*
- *Design Output*
- *Design History File*

Historical Perspective

- 1976 - MEDICAL DEVICE AMENDMENTS passed to ensure safety and effectiveness of medical devices. The amendments require manufacturers to register with FDA and follow quality control procedures.
- 1978 - 21 CFR 820- GMP Regulation for Medical Devices Added
- GAO review of device recalls shows 44% of device problems due to design deficiencies.
- 1989 - FDA's "Preproduction Quality Assurance Planning" document outlines design controls recommendations.

Historical Perspective, cont..

- 1990 - SAFE MEDICAL DEVICES ACT of 1990 gives the FDA the authority to establish “design validation” (I.e.. design controls)
- 1995 - GMP draft revision published in Federal Register
- 1996 - GMP final rule published in Federal Register
- June, 1997 - GMP final rule becomes effective. FDA will audit design controls but will not enforce. No 483 observations for design controls.
- June, 1998 - ENFORCEMENT OF DESIGN CONTROLS BEGINS!

Part 820 is not rocket science.

- *It is written in plain English that all of you can understand.*

Terminology: Acronym Alert ! (1)

- *GMP: Good Manufacturing Practices.*
- *DMR: Device Master Record: means a compilation of records containing the procedures and specifications for a finished device.*
- *DHR: Device History Record means a compilation of records containing the production history of a (particular) finished device.*
- *DHF: Device History File means a compilation of records which describes the design history of a finished device.*

Terminology: Acronym Alert ! (2)

- *FMEA: Failure Modes and Effects Analysis, an inductive "bottom up" analysis technique.*
- *FMECA: Failure Modes, Effects, and Criticality Analysis includes a risk ranking to the above (probability and severity)*
- *FTA: Fault tree analysis, a "top down" deductive approach to failure mode analysis.*
- *ISO: International Organization for Standards is a worldwide federation of national standards bodies. They prepare international standards through technical committees.*
- *PEMS: Programmable Electrical Medical Systems*

Terminology: Acronym Alert ! (3)

- *ISO-9001: "Quality Systems - Model for Quality Assurance in Design, Development, Production, Installation, and Servicing." Revised in 1994 and now an American National Standard. (Other standards in this series do not include design & development.) This standard was used as a model for FDA's revision of the GMP regulation.*
- *SMDA: Safe Medical Device Act of 1990*
- *BOM: Bill of Material. List of component parts of a device or subassembly.*
- *ESD: Electrostatic Discharge*
- *EMI: Electromagnetic Interference*

Terminology:

- *Labeling: To the FDA, means device labels, user manuals, advertising, any printed matter re the device.*
- *Murphy's Law: Anything that can go wrong, will, and at the worst possible time.*
- *Establish means define, document (in writing or electronically), and implement.*

Why institute design controls?

- *1.*
- *2.*
- *3.*

Design Controls: Requirements Overview

- *Throughout the GMP, the terms "establish and maintain" and "designated individual(s)" appear.*
- *What do these terms this mean?*
- *Establish means: Define, document (in writing or electronically), and implement.*
- *Maintain means: (1.) Distribute the documents to the appropriate people (2) Train people in their use and (3) Keep them up to date. See document control section of the GMP 820.40 for other requirements.*
- *Designated individuals means people who are qualified to perform the task assigned and are expressly given the authority and responsibility company management. (Org. Chart)*

Comparison of ISO-9001 to 21CFR820.30 (Design Controls)

ISO-9001 - 4.4 Design Control	*820.30 Design Controls*
4.4.1 General	(a) General
4.4.2 Design and development planning. 4.4.3 Organizational and technical interfaces	(b) Design and development planning.
4.4.4 Design input	(c) Design input
4.4.5 Design output	(d) Design output.
4.4.6 Design review	(e) Design review.
4.4.7 Design verification	(f) Design verification.
4.4.8 Design validation	(g) Design validation.
	(h) Design transfer.
4.4.9 Design changes	(i) Design changes.
4.16 Quality records	(j) Design history file.

Design Controls: Requirements Overview: 21 CFR 820.30

- *(a) General: Need written procedures to control the design of the device so that design requirements are met. Applies to all Class II & III devices, and class I devices with software.*
- *(b) Design & Development planning. Written plans describing the activities and responsibilities. Describe group interfaces.*

Design Controls: Requirements Overview: 21 CFR 820.30

- *(c) Design input. Procedures to insure design requirements are appropriate. Written device design requirements.*
- *(d) Design output. Procedures for defining/documenting design output to assure conformance with input requirements.*

Design Controls: Requirements Overview: 21 CFR 820.30

- *(e) Design review. Procedures to conduct design reviews. Representatives of all functions concerned..*
- *(f) Design verification. Procedures for verifying device design. Confirm design meets input requirements. Written and approved results for DHF.*

Design Controls: Requirements Overview: 21 CFR 820.30

- *(g) Design validation. Procedures for validation of design. Actual or simulated use tests. Software validation. Risk analysis. Documented results for the DHF.*
- *(h) Design transfer. Procedures to ensure creation of proper production specifications.*

Design Controls: Requirements Overview: 21 CFR 820.30

- *(i) Design changes. Change control procedure required. Written approval required for changes prior to implementation.*
- *(j) Design history file. Records to show device developed in accordance with design plan*

Verification Vs. Validation..

- *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.
- *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be *consistently* fulfilled.

Summary: Requirements for Documentation of Design Controls

- *1. Device design control procedure(s) (Product development protocol)*
- *2. Specific Device development activity plan with defined responsibilities for implementation and description of interfaces. A living document which evolves and gets reviewed and approved. Goes into DHF for this device.*
- *3. Design input procedures to ensure that design requirements are appropriate.*
- *4. Design input requirements document for specific device.*

Summary: Requirements for Documentation of Design Controls

- *5. Procedures for defining design output.*
- *6. Actual design output (approved, signed, and dated)per procedure above. Allows evaluation of conformance to design input requirements (to DHF) The total finished design output consists of the device, its packaging and labeling, and the device master record.*
- *7. Procedures for design reviews.*
- *8. Actual results of design reviews (to DHF)*
- *9. Procedures for design verification.*
- *10. The results of design verification (to DHF)*

Summary: Requirements for Documentation of Design Controls

- *11. Procedures for design validation.*
- *12. The results of design validation (to DHF)*
- *13. Procedures for design transfer.*
- *14. Procedures for change control.*
- *15. A DHF, design history file, contains or references records to demonstrate the design was developed in accordance with approved design plan.*

Design and Development Planning

- *There were 8 generic procedures required. All except one (change control) could be incorporated into a Product Development Protocol. (or Development SOP)*
- *In the alternative, Design review and Transfer to production could have their own procedures.*

A word about procedures...

- *Keep them simple, short and to the point, or they will not be followed. Failure to follow own procedures may result in a "483" observation*
- *<u>Train</u> employees in use of the procedures.*

Product Development Protocol: Areas which need to be addressed

- *Risk analysis*
- *Design Input*
- *Design Output*
- *Design Review*
- *Design Verification*
- *Design Validation*
- *Design Transfer*
- *Design Changes (within development)*
- *Interfaces (inter-departmental)*

Design Input

- *Design specifications should be established before any significant design activity begins.*
- *We will call design specifications the "Product Requirements Document."*
- *Number each requirement with a unique designator. This will help us later on during verification/validation.*

Product Requirements Document

- *This document shall be approved by designated individuals, such as:*
- *Marketing*
- *Engineering*
- *Regulatory/Quality*
- *Manufacturing*
- *Management*
- *Purchasing*

Product Requirements Document should address:

- *Identity of product*
- *Performance characteristics*
- *Classification*
- *Physical characteristics*
- *Environmental characteristics*
- *Major components*
- *Safety & performance considerations*

Product Requirements Document sources of information:

- *Competitive products*
- *Focus groups of potential users*
- *FDA guidance documents which give 510(k) or other product requirements*
- *Trade shows*
- *Catalogs*

Product Requirements Document

- *It's a "living" document which evolves as the product is being developed.*
- *Keep previous editions for the DHF.*
- *Number each paragraph or significant requirement.*
- *Class exercise: create a product requirements document for hypothetical product. (Will be used later..)*

Project Development Plan

- *Project tasks phases are identified (Pert or Gantt chart)*
- *Project tasks are assigned to designated individuals*
- *Timelines and cost targets may be included.*
- *Requires approvals*
- *Keep up to date and keep old versions for DHF.*

Human Factors

- *Many device problems have been found to be a result of poor understanding of human factors. Patient deaths have occurred as a result. Example: unprotected electrodes*
- *Problems: Device use errors - improper hook ups, improper device settings*
- *Solutions: "Ergonomic or Human factors engineering - See "Do it by Design" and AAMI Human Factors Engineering Guidelines.*

Design Reviews

- *Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.*
- *Reviews should occur at pre-planned check points during design progress and can also be called for ad-hoc problem solving.*

Design reviews

- *Minutes of design reviews should be recorded and include:*
- *moderator and attendees,*
- *date and design phase/stage*
- *plans and/or agenda,*
- *problems and/or issues to identify and solve*
- *minutes and reports, and*
- *follow-up report(s) of solutions and/or the next review covers the solutions and remaining issues*
- *Minutes are kept in the DHF.*

Design Output

- *Design output per 820.3(g) means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.*
- *Device master record (DMR) means a compilation of records containing the procedures and specifications for a finished device.*

Design output requirements

- *Ability to determine conformance to product requirements specification.*
- *Acceptance criteria*
- *Written, reviewed, and approved prior to release to production.*
- *What about partial releases?*

Design History File: Contents, creation, management.

- *Required by 820.30 (j)*
- *Proof that product was developed according to plan and requirements.*
- *Important: needed for regulatory submissions! 510(k), PMA.*
- *Documents are never created just to go into the DHF*

Design history file: contents

- *All versions of product requirements documents.*
- *All versions of Development plans (Pert, Gantt, etc..)*
- *Minutes and other documentation of design reviews.*
- *Verification and validation plans and results.*
- *Preliminary design drawings, schematics, software, and the like.*

Design history file contents, continued

- *Test reports such as EMI, ESD, electrical safety, radiation leakage, and the like. Records of team meetings*
- *“Significant engineering documents”*
- *“Annotated copies of verified labeling, printouts, etc.. and associated notes and any checklists”*
- *After device release, any significant changes, including associated validation.*
- *Engineers’ log books or an index of where to find them.*

Log books:

- *Best to use bound books with numbered pages; write in ink; sign & date every page. Helps substantiate patent claims.*
- *Create an index to Engineers' log books, serialize them.*

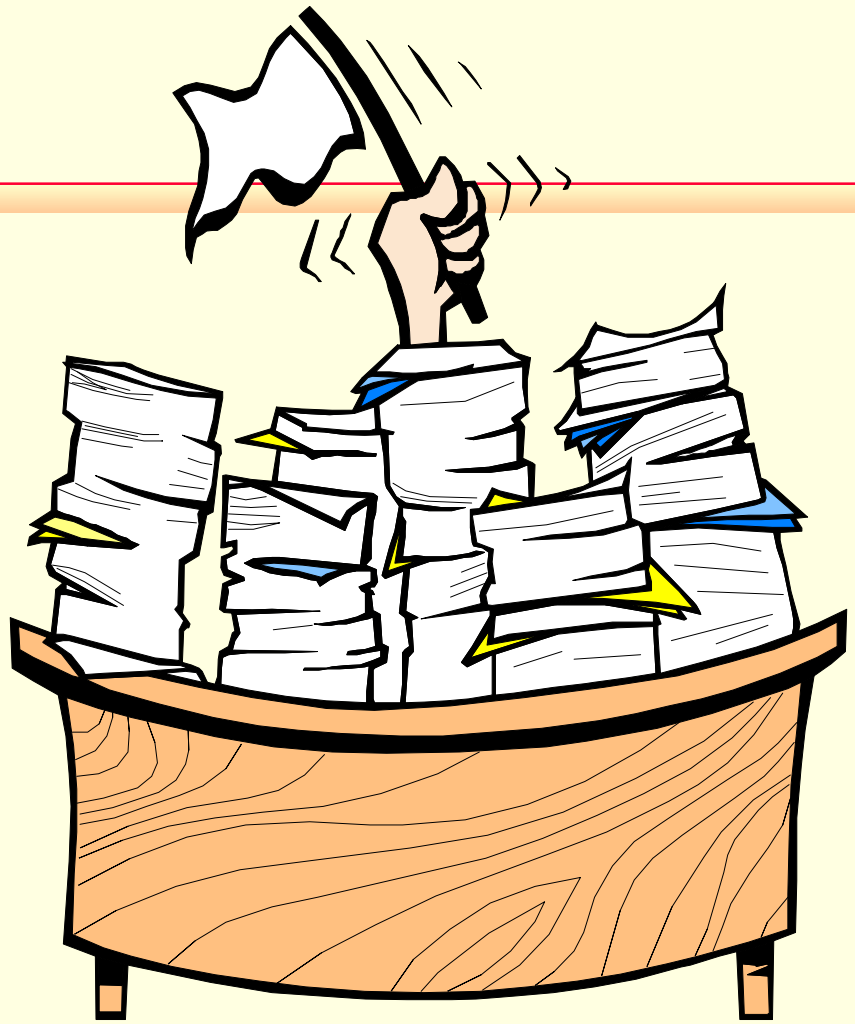
Design history file: creation, management.

- *(Documents are not created just for DHF) Creation refers to the need to index and track required documents, and assure creation for fulfilling the project plan.*
- *Management of the file should be an assigned task. Indexing (ie noting the location) and making copies to assure file completeness is needed.*

Recap:

- *History*
- *Terminology*
- *Overview*
- *Design & Development Planning*
- *Design Input*
- *Design Reviews*
- *Design Output*
- *Design History File*

What is meant by this?



Recap of Today's Topics

- *Introduction - Historical.. Why design controls?*
- *Requirements Overview..*
- *Design and Development Planning*
- *Design Input*
- *Design Reviews*
- *Design Output*
- *Design History File*

Today's topics:

- *Design Verification and Validation*
- *Design Transfer*
- *Change Control*
- *Tools for Assuring Device Safety*
- *FMEA*
- *510(k)*

Design Verification and Validation

- *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled. Design output meets *design input requirements.*

- *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be *consistently* fulfilled. Design conforms to *user needs and intended uses.* Done on initial production units under simulated or actual use conditions.

Design Verification

- *Most important point: A requirements traceability matrix to ensure test coverage of all product requirements.*
- *Using the product requirements document we previously created, generate a "requirements traceability matrix" for our verification project phase.*
- *Verification shall show that results meet requirements. Store in DHF.*

Design Validation

- *(Distinguish from Process Validation)*
- *Validation procedures must be written.*
- *Performed under defined operating conditions and simulated or actual use conditions, on initial production units, lots, batches, etc.*
- *Includes software validation and risk analysis.*
- *Tests designed to “stress the limits”..*

Design validation: tests -

- *Temperature/humidity*
- *EMI & ESD*
- *Safety*
- *User tests*
- *Packaging*
- *Labeling*

Design Transfer (to Manufacturing)

- *Subsections may be transferred before entire design is complete.*
- *Production specifications are what is transferred. They constitute the DMR*
- *These include: BOM's, schematics, assembly drawings, assembly instructions.*

Change Control

- *It is usually appropriate to have a separate written change control procedure.*
- *Once a design is transferred to production, change control must be used. A separate change control procedure (perhaps less formal) may be used prior to transfer.*

Change control: key points -

- *Validation and/or verification of the change required prior to implementation*
- *Review and approval required.*
- *Sec. 820.40 addresses document changes. Since the DMR consists mainly of documents, this rule applies.*
- *Beware of "sneak" DMR changes….*
- *Very common problem: Unapproved DMR documents.*

Tools for assuring device safety- Risk or Hazard Analysis Tools.

- *Risk Analysis called for in Product Development Protocol per FDA's Inspectional Strategy*
- *Preproduction Quality Assurance Planning and is often required in 510(k) submissions.*
- *Performing Risk Analysis is a defense to product liability suit.*

Other Safety tools: Adherence to Safety Standards

- *IEC 601-1, Medical Electrical Equipment Part 1: General Requirements for Safety*
- *IEC 513, Fundamental aspects of safety standards for medical electrical equipment*
- *IEC 601-1-4, Safety Requirements for Programmable Electronic Medical Systems*
- *IEC 825, Procedures for failure modes and effects analysis*
- *IEC 1025, Fault Tree Analysis*
- *IEC EN 1441, Medical Devices - Risk Analysis*
- *UL Safety Standards*
- *AAMI Standards*
- *US Govt. Performance Standards 21CFR10xx.*

General Risk or Hazard Analysis Tools

- *Fault Tree Analysis (top down analysis)*
- *FMEA and FMECA: Failure Modes and Effects Analysis, Failure Modes Effects and Criticality Analysis. (bottom up analysis)*
- *FMECA includes criticality analysis, or level of severity and probability of failure. MIL-STD-1629*

Issues to consider:

- *Human Error: Manufacturing operation, Operator, Home User, Service Person*
- *Software Error*
- *Electronic Component Failure*
- *Mechanical Component Failure*
- *Normal wear-out*
- *Murphy's Law*

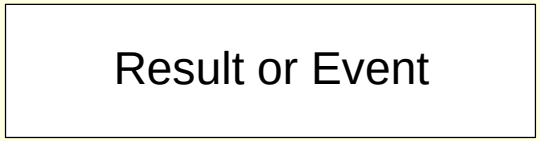
Hazard Analysis Process

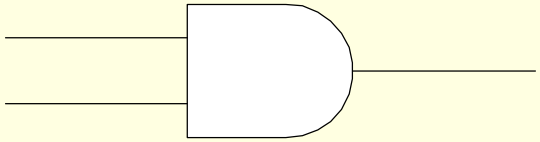
- *Identify Hazards via formal process (FTA and/or FMEA)*
- *Evaluate (probability and severity) and define mitigation*
- *Implement and verify mitigation*
- *Review in light of complaint files and repair records.*

Fault Tree Analysis (top down, deductive)

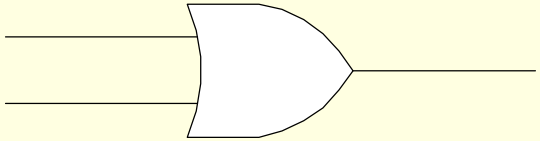
- *1. List the possible hazards, such as: Fire, electrical shock, mis-diagnosis, injury, etc.*
- *2. What failures, or combination of failures, will lead to the named hazards?*
- *3. Diagram the fault tree.*
- *4. Use the tool to intercept or design out unacceptable consequences.*

Fault Tree Analysis: symbols





"AND" gate



"OR" gate

FMEA: Failure Mode and Effects Analysis

- *A bottom up, inductive approach.*
- *System FMEA Vs Design FMEA.*
- *Design FMEA looks at product as a unit and examines failure potentials at the core levels of a device.*
- *Examine each component and its failure mechanism. For software and hardware*
- *A systematic data sheet approach is employed*

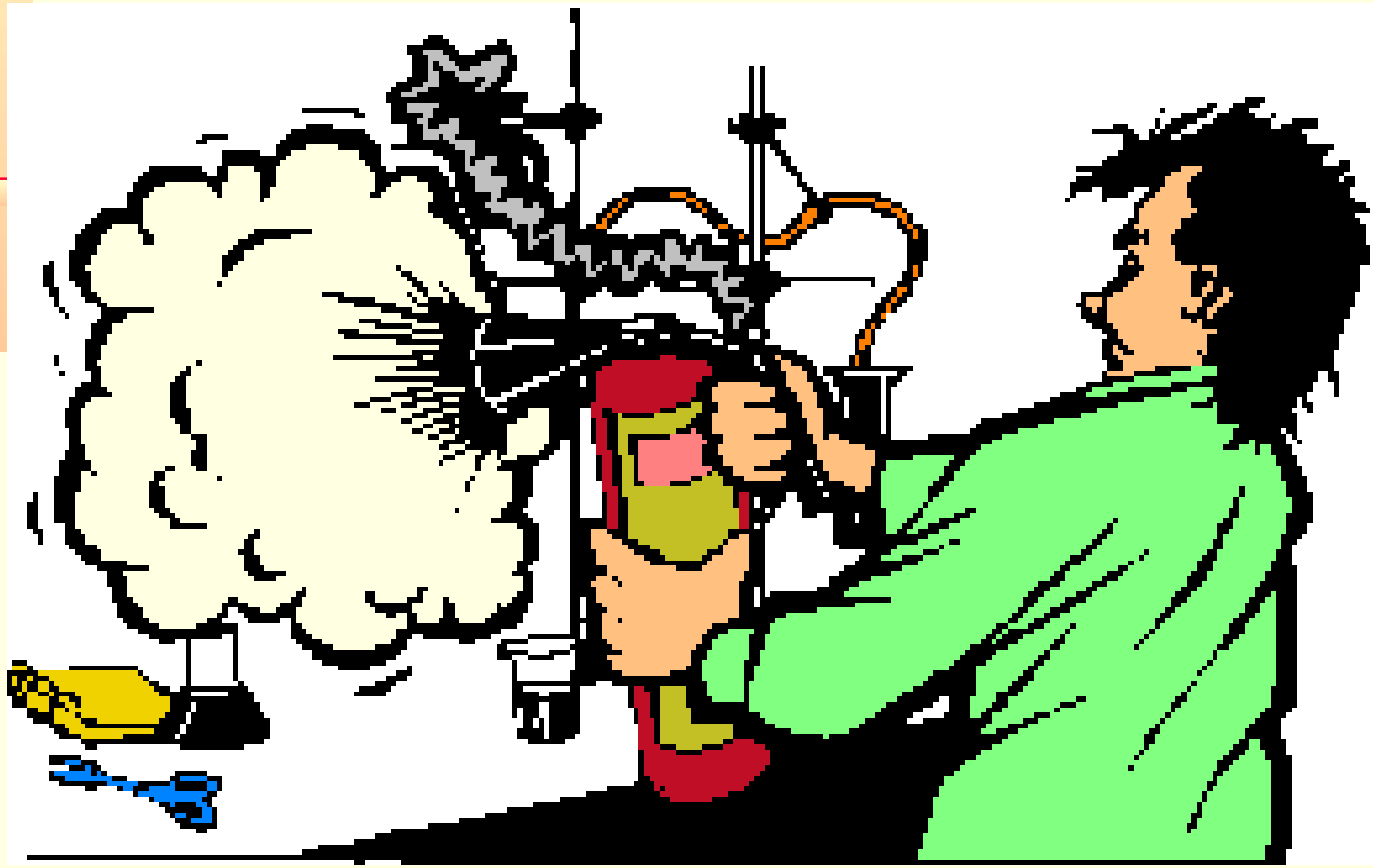
FMEA

Function or Component	Failure Mode	Effect on System	Possible Hazards	Risk Index	User Detection Means	Applicable Control

Risk Index Table

Probability of Occurrence	Severity I Catastrophic (Death, serious injury)	Severity II Significant (Reversible serious injury)	Severity III Marginal (Incon-venience)	Severity IV Negligible
Frequent	**1**	**3**	**7**	**13**
Probable	**2**	**5**	**9**	**16**
Occasional	**4**	**6**	**11**	**18**
Remote	**8**	**10**	**14**	**19**
Improbable	**12**	**15**	**17**	**20**

Safety testing



Safety Testing Overview: Electrical safety

- *Applicable standards: UL-544 (Being replaced by UL-2601= IEC-601, AAMI SCL (Safe Current Limits) IEC-601 - Medical electrical equipment - General requirements for safety*
  Tests covered - Prevention against electrical shock:
- *Ground resistance*
- *Chassis leakage*
- *High-voltage breakdown*
- *Patient connection leakage - sink and source*
- *Why?*

Safety Testing Overview:

Other sections in IEC-601:

- *Identification & marking requirements*
- *Environmental - operating and storage*
- *Mechanical hazards*
- *Excess radiation*
- *Flammable anesthetics*
- *Excessive temperatures and other hazards; ESD, fire, leakage, pressure, human error*
- *Accuracy of operating data and protection against hazardous output*
- *Fault conditions*
- *Constructional requirements*

Safety Testing Overview: EMI per FDA recommendation

- *EMC radiated and conducted according to CISPR 11*
- *Magnetic low frequency emissions per RE101, MIL-STD-462D (if concerned about health effects..)*
- *ESD per IEC-801-2 +/- 8KV Air, +/- 6KV Contact*
- *AC voltage fluctuations, transients, and surges*
- *See tabs 13, 14, and 15.*
- *Why?...*

Safety testing:

- *The FDA has numerous documents available via Facts-On-Demand Fax back service, 1-800-899-0381.*
- *These documents give details, in many cases, on what safety and effectiveness testing the FDA expects to see in submissions.*

510(k): Getting the device to market

- *Many of the documents generated under design controls will be needed for the 510(k) - A pre-market notification required for most devices.*
- *Device classes - Three general categories with increasing regulatory requirements necessary to assure safety and effectiveness..*

510(k): Getting the device to market - submission components-

- *General Information - Identification*
- *Proposed labeling, labels, advertisements, users manuals*
- *Intended uses*
- *Comparison to legally marketed device*
- *Diagrams, engineering drawings, photographs*
- *more...*

510(k): Getting the device to market - submission components-

- *Performance data: bench, animal, clinical (from verification and validation!)*
- *Software validation and verification.*
- *Biocompatibility & Sterility Information*
- *Conformance to standards certifications such as UL, IEC, others.*
- *The information in the DHF and DMR feeds directly into the 510(k) submission*

Recap..

- *Design verification and validation*
- *Design transfer*
- *Change control*
- *Tools for assuring device safety - FMEA, etc.*
- *Safety testing*
- *The 510(k)*

Today's topics:

- *Software validation*
- *Process validation*
- *Wrap-up and open discussion*

Software validation

- *This topic has attracted the attention of the FDA because of problems which have led to patient deaths, among other reasons.*
- *Case in point: The Therac-25*
- *11/13/89: FDA's Draft Policy for regulation of computer products (medical devices)*

Software validation

- *1990: Application of Medical Device GMPs to computerized devices and manufacturing processes.*
- *1991: Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) review.*
- *1996: ODE Guidance for Medical Devices Containing Software (Draft) Relies on IEC-601-1-4*

Software validation

- *IEC 601-1-4 Medical electrical equipment Part 1: General Requirements for Safety 4. Collateral Standard: Programmable electrical medical systems (PEMS)*
- *Useful section of Draft Guidance: Appendix C. Review Checklist and Common Requests (of 510(k) reviewers)*

Software validation: Concepts - System Development Life Cycle

- *Initiation phase*
- *Requirements analysis phase*
- *Design phase*
- *Programming and testing phase*
- *Integration and system test phase*
- *Validation phase*
- *Operations and maintenance phase*
- *Retirement phase*

Software emphasis: Risk Management

- *ODE Guidance: sec. 2.1:*
- *Distinct phases for work*
- *Feedback among phases*
- *V & V activities look for sources of error*
- *Development lifecycle and risk management fully integrated. See ODE guidance fig. 2-1*
- *Again, level of concern fig. 3-1*

FDA's expectation: Appendix C - Review Checklist

- *Hazard Analysis*
- *Safety incorporated*
- *Appropriate methodology*
- *Verification and Validation prior to release?*
- *Traceability? (to requirements)*
- *Change control*
- *Other - hazardous functions limited only by software (Therac-25!)*

Vendor supplied software

- *Needs to be qualified by company. Amount of qualification varies.*
- *Need version control of vendor supplied software.*
- *Applies to vendor supplied firmware as well: BIOS for example.*
- *Attempt to obtain assurance that vendor used a quality process in development*
- *Once validated, carefully control the version*

Software checklists

- *Software GMP Questions*
- *Software Assessment Questionnaire (possible model for internal audit)*
- *Software questions for 510(k) submissions*
- *IEEE Std 1012-1986; Std 729-1983*

Process validation: IQ, OQ, PQ.

- *Typical application: Manufacturing process which is not 100% inspected, such as wave soldering.*
- *IQ means Installation Qualification. Was machine installed according to manufacturers' requirements? Establish maintenance and calibration requirements. Secure manuals. Write work instructions.*

Process validation: IQ, OQ, PQ.

- *OQ means Operational Qualification. The machine is operated. Does it perform according to manufacturers' claims?*
- *PQ means Process Qualification. The machine is tested with your product with an eye to stressing the limits of the process : high/low temperature, high/low conveyer rate, etc.*
- *Can the manufacturing process consistently produce product meeting requirements?*

Open discussion. Sources for additional help

- *FDA's World Wide Web Site: www.fds.gov/*
- *ASQC*
- *IEC standards*

Course wrap up