Design Controls

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This communication is consistent with 21 CFR 10.85(k) and constitutes an informal communication that represents my best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the Agency to the views expressed.

Presentation Outline

1) Design Control Fundamentals
2) Design Control FDA 483 Statistics
3) 2nd most frequent 483 item - Design Validation
4) 3rd most frequent 483 item - Risk Analysis
5) Summary

Design Validation - Definitions

- **[Design] Verification** means confirmation by examination and provision of objective evidence that **specified [design] requirements** have been fulfilled; see 21 CFR 820.3(aa);
  - Versus
- ***Design Validation*** means establishing by objective evidence that device specifications conform with **user needs** and **intended use(s)**; see 21 CFR 820.3(z)(2)

Design Validation – The Regulation

- “Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF;” see 21 CFR 820.30(g).

Design Validation - Preamble

- Comment #65
  - IDE Devices must follow the Design Control Regulation
- Comment #68
  - All devices automated by software must be validated (including Class I); 21 CFR 820.30(a)

Design Validation - Preamble

- Comment #80 & #85
  - DV ideally involves actual production units or their equivalents w/ justification; see 21 CFR 820.30(g)
- Comment #81
  - Design Validation must be performed, as Verification alone not sufficient; the two activities are distinct
- Comment #82
  - Design Output must be both Verified and Validated; see 21 CFR 820.30(f) & 21 CFR 820.30(g)

Design Control FDA 483 statistics

Reference Number	Short Description	FY19 Total
21 CFR 820.30(i)	Design changes	54
21 CFR 820.30(g)	Design validation	51
21 CFR 820.30(g)	Risk analysis not performed/inadequate	48
21 CFR 820.30(f)	Design verification	37
21 CFR 820.30(e)	Design review	27
21 CFR 820.30(j)	Design history file	27
21 CFR 820.30(c)	Design input	21
21 CFR 820.30(d)	Design output	14
21 CFR 820.30(h)	Design transfer	14
21 CFR 820.30(b)	Design plans	7

FY19 Data obtained on 7/24/2020 from:
https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

Design Validation FDA 483 statistics

Most Common Design Validation 483s	FY19 Count
User needs and intended uses	11
Software validation not performed	7
Software validation documentation	7
Acceptance criteria	6
Production units	6
Simulated testing	5
Documentation	5

FY19 Data obtained on 7/24/2020 from:
https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspection-observations

D. Validation – Areas for Improvement

- #1 Design validation 483 item - user needs and intended uses
  - User needs, intended use and/or intended use environment not properly understood/characterized
  - DVs not conducted under defined operating conditions, simulated and/or actual use conditions.

D. Validation – Areas for Improvement

- #2-3 Design validation 483 item – software (sw) validation not performed/documented
  - "Design validation shall include software validation and risk analysis, where appropriate"; 21 CFR 820.30(g)
  - All Class I Devices automated by software and Class II+ devices require sw Validation; 21 CFR 820.30(a)
  - Black vs. White Box sw Validation; see preamble comment #136

D. Validation – Areas for Improvement

- #4 Design validation 483 item – acceptance criteria
  - Clearly defined in a pre-approved DV protocol
  - Objective/quantitative metrics for acceptance criteria
  - The acceptance criteria should be achieved by the Design Validation

D. Validation – Areas for Improvement

- #5 Design validation 483 item – production units
  - DV must be performed on initial production units, lots, or batches, or their equivalents; see 21 CFR 820.30(g)
  - Most commonly demonstrated by DHRs, which link the DMR to the specific units (S/Ns) used in the DV
  - Justification for use of non-production units in DV, must explain equivalency (not easy!)

D. Validation – Areas for Improvement

- #6 Design validation 483 item – simulated testing
  - DVs not conducted under simulated and/or actual use conditions.
  - DV User population should roughly match intended user population
  - DV/usability study should challenge the device's labeling

D. Validation – Areas for Improvement

- #7 Design validation 483 item – documentation
  - Document or provide traceability to all DV activities
    - Many include non-traditional quality system records (e.g. lab notebooks, excel spreadsheets and etc.)
    - Investigators should review the raw data in addition to the summary report
  - Signatory Approvals
    - Quality Review
    - DV Protocol approved BEFORE execution of the DV
    - Acceptance Criteria achieved during the DV

Risk Management - Regulatory Basis

- Only mention in the cGMPs: “Design validation shall include software validation and risk analysis, where appropriate”; 21 CFR 820.30(g).
- ISO 14971:2019 Risk Management in DCs
  - TIR24971:2020 Guidance Document
  - Risk Management File = “living-history document” that accounts the risk management plan for a particular device or device family

Risk Management- ISO 14971

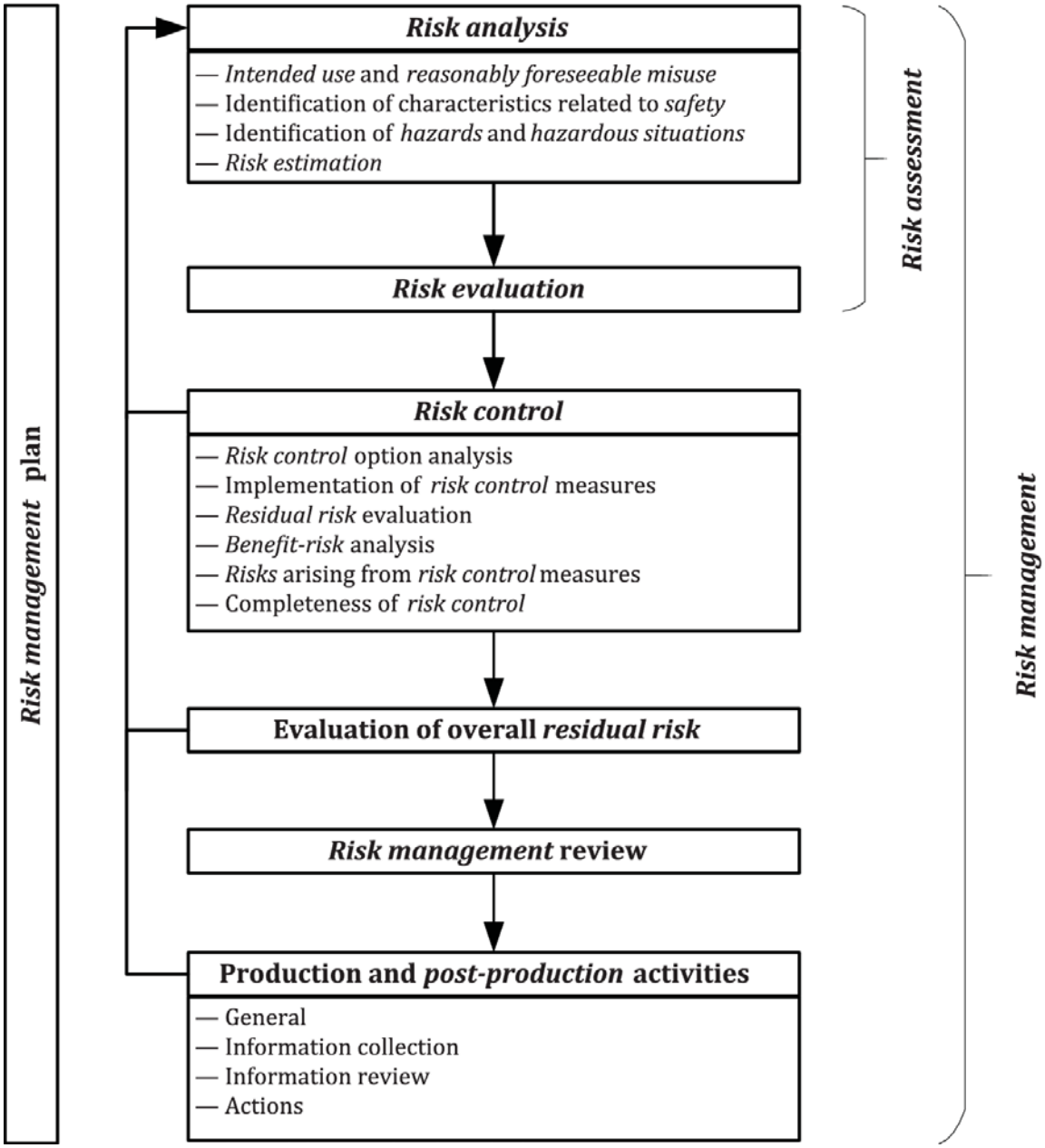

Image from: American National Standard. (2019). *ANSI/AAMI/ISO 14971: 2019 Medical devices—Application of risk management to medical devices*

Risk Management - Preamble

- Preamble Comment #81 – Risk & Design Validation
  - "The extent of [DV] testing conducted should be governed by the risk(s) the device will present if it fails."

Risk Management - Preamble

- Preamble Comment #83 – Risk Management Process
  - "manufacturers are expected to identify possible hazards associated with the design in both normal and fault conditions. The risks associated with the hazards, including those resulting from user error, should then be calculated in both normal and fault conditions. If any risk is judged unacceptable, it should be reduced to acceptable levels by the appropriate means, for example, by redesign or warnings. An important part of risk analysis is ensuring that changes made to eliminate or minimize hazards do not introduce new hazards. Tools for conducting such analyses include Failure Mode Effect Analysis [FMEA] and Fault Tree Analysis, among others."

Risk Management - Preamble

- Preamble Comment #121 - “the manufacturer should perform risk analysis first on the finished device, and subsequently on the components of such device, to determine the need for [critical device component] traceability”
- Preamble Comment #159 – Risk & CAPA
  - The degree/extent of CAPA activities should be commensurate to the magnitude of the non-conformance and risk level.

Risk Management – Areas for Improvement

- #1 – Risk analysis not performed/inadequate
- Solution: Fully execute the Risk Management Plan
  - Risk Analysis
  - Risk Evaluation
  - Risk Control
  - Evaluation of Overall Residual Risk
  - Risk Management Review
  - Production and Post-Production Activities

Risk Management – Areas for Improvement

- #2 – Risk Analysis is not “live”
- Solution: Periodically assess your RA(s) for accuracy relative to hazards manifesting in the field and their respective frequency of occurrence and/or severity. Update RA with new hazards identified and/or values, as needed.

Summary

- Top 483 citations in FY19:
  - #1 Design Changes
  - #2 Design Validation
  - #3 Risk Analysis
- DV - testing actual production units with a representative user population (stats) in simulated use setting, according to a preapproved protocol. The results should be documented in the DHF.

Summary

- Risk Management at a high-level:
  - Risk Assessment: Characterize Initial Risk
    - Identify Intended use, reasonably foreseeable misuse, safety characteristics, hazards and risk estimation
  - Risk Control
    - Analyze/implement risk controls, residual risk evaluation, benefit-risk analysis and risks arising from control measures.
  - Evaluation of overall residual risk

Summary

- Risk Analysis at a high-level (continued):
  - Risk Management Review
    - Resolution of any outstanding risk management-related issues
  - Production and post-production
    - Monitor quality data for changes in risk components
    - Update Risk Analysis/Management File as needed
    - Various situations detected at this stage may result in action(s)/CAPA(s)

QUESTIONS?

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