Asia-Pacific Economic Cooperation

USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
DK Kim International Center for Regulatory Science

GLOBAL STRATEGIC SOLUTIONS™

How Do Quality Standards (ISO 14971:2019 and Application of Risk Management) De-Risk Devices?

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Who is David R Rutledge

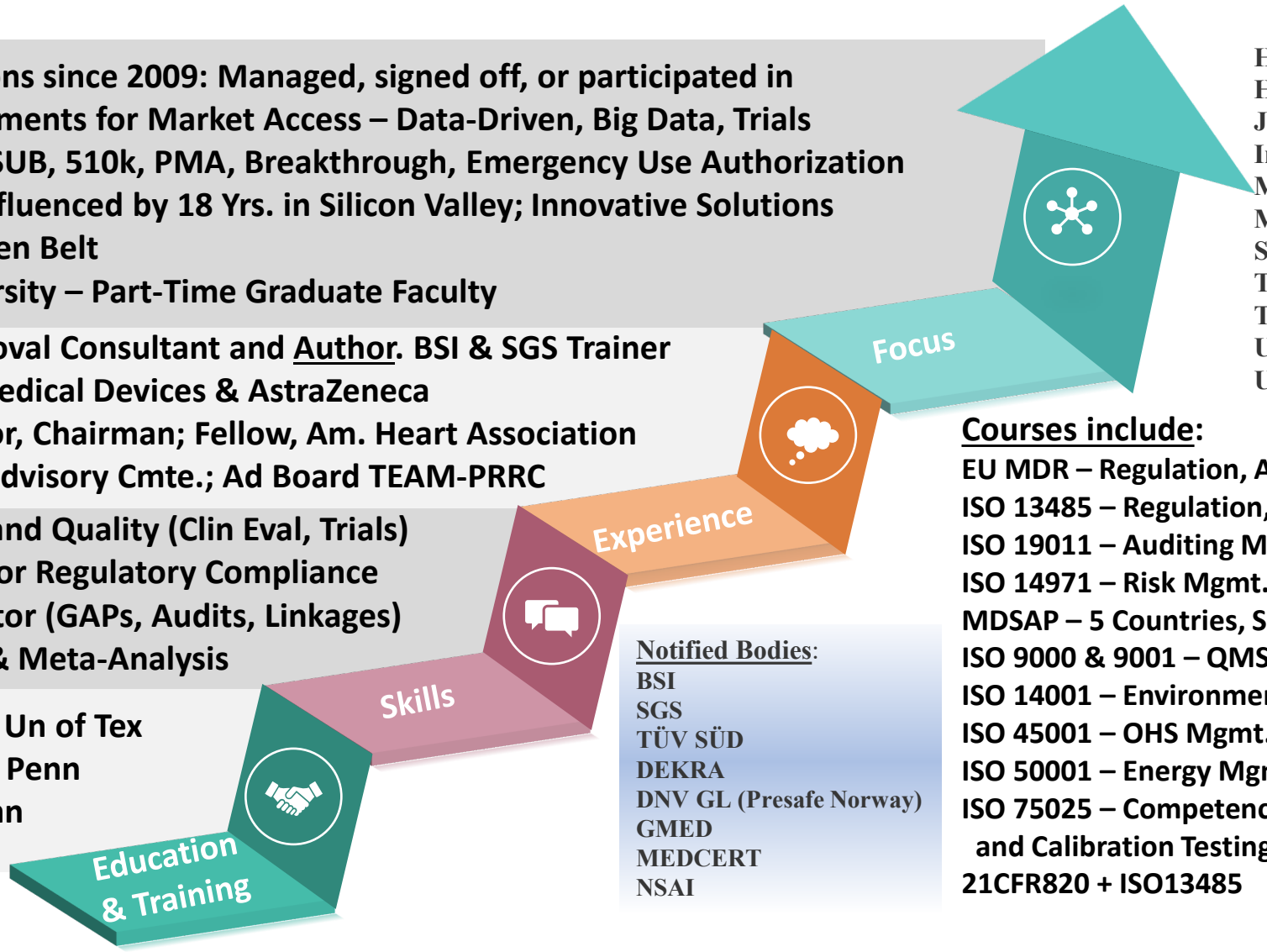
Geographic Areas
Australia TGA
Brazil ANVISA
China NMPA
EU/EMA
S Korea Min of Food & Drug Safety
Health Canada
Hong Kong
Japan PMDA
India CDSCO
Malaysia
Mexico COFEPRIS
Saudi FDA
TAIWAN FDA
Thailand FDA
UK MHRA
US FDA

4
977 Clinical Evaluations since 2009: Managed, signed off, or participated in
Clinical Data Requirements for Market Access – Data-Driven, Big Data, Trials
US FDA – e-STAR: Q-SUB, 510k, PMA, Breakthrough, Emergency Use Authorization
Technology User – Influenced by 18 Yrs. in Silicon Valley; Innovative Solutions
Lean Six Sigma – Green Belt
San Jose State University – Part-Time Graduate Faculty

3
Global Product Approval Consultant and Author. BSI & SGS Trainer
Director at Abbott Medical Devices & AstraZeneca
Tenured Full Professor, Chairman; Fellow, Am. Heart Association
Industry Rep – FDA Advisory Cmte.; Ad Board TEAM-PRRC

2
Clinical, Regulatory, and Quality (Clin Eval, Trials)
Person Responsible for Regulatory Compliance
ISO 13485 Lead Auditor (GAPs, Audits, Linkages)
Systematic Reviews & Meta-Analysis

1
BS Pharm, Pharm.D., Un of Tex
Residency, Hos of Un Penn
Fellowship, Un of Tenn



Notified Bodies:
BSI
SGS
TÜV SÜD
DEKRA
DNV GL (Presafe Norway)
GMED
MEDCERT
NSAI

Courses include:
EU MDR – Regulation, Auditor
ISO 13485 – Regulation, Lead Auditor
ISO 19011 – Auditing Mgmt. Systems
ISO 14971 – Risk Mgmt.
MDSAP – 5 Countries, Single Audit
ISO 9000 & 9001 – QMS
ISO 14001 – Environment Mgmt. System
ISO 45001 – OHS Mgmt. System
ISO 50001 – Energy Mgmt. System
ISO 75025 – Competency of Testing and Calibration Testing
21CFR820 + ISO13485

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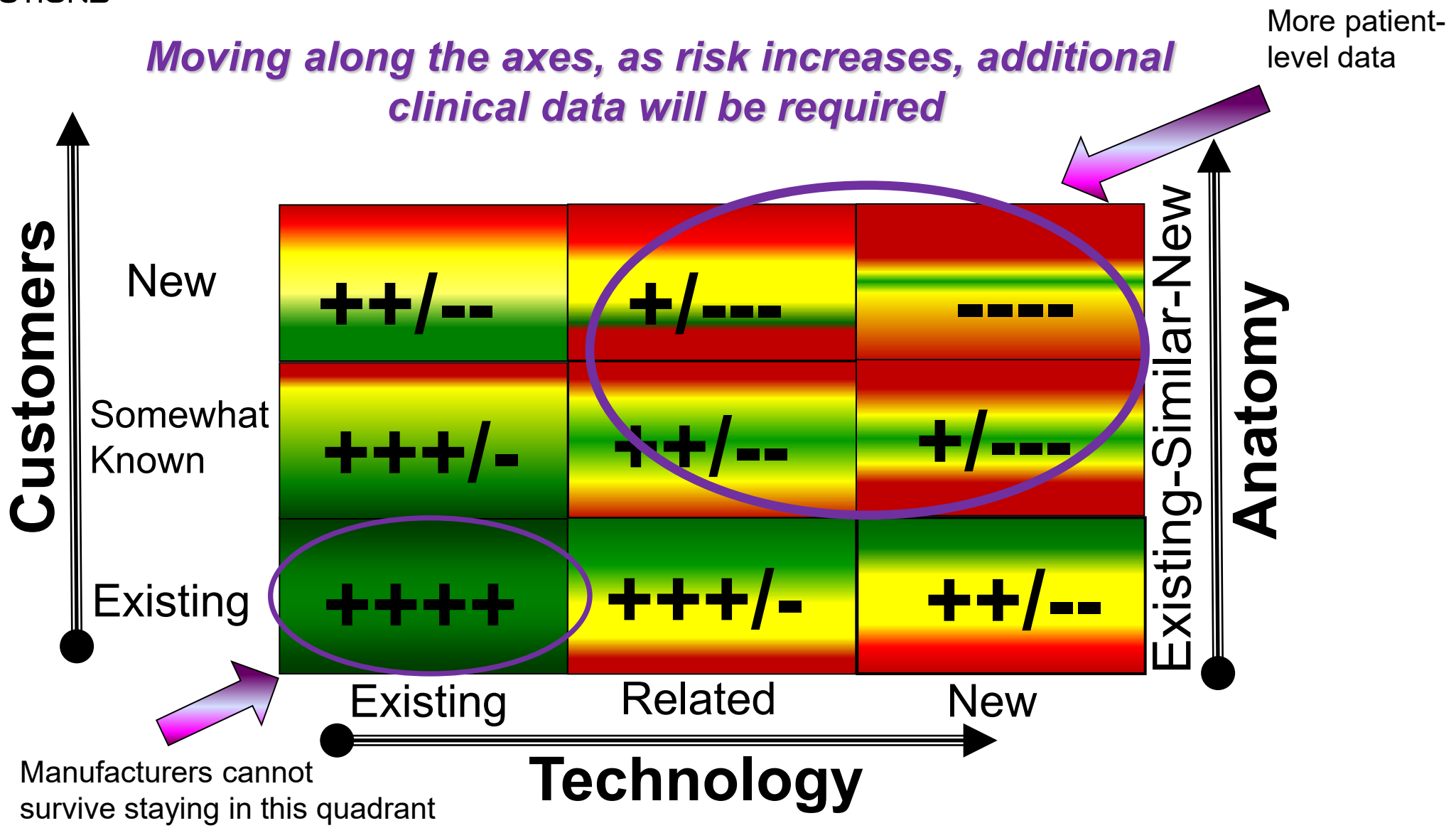
Customers-Technology-Anatomy

Moving along the axes, as risk increases, additional clinical data will be required



ISO 14971:2019
How To View This Presentation

This presentation can be viewed through **4 lenses**

1. Regulators and Notified Bodies
2. Manufacturers
3. Patients
4. Healthcare Professionals

ISO 14971:2019

EN ISO 14971:2019*

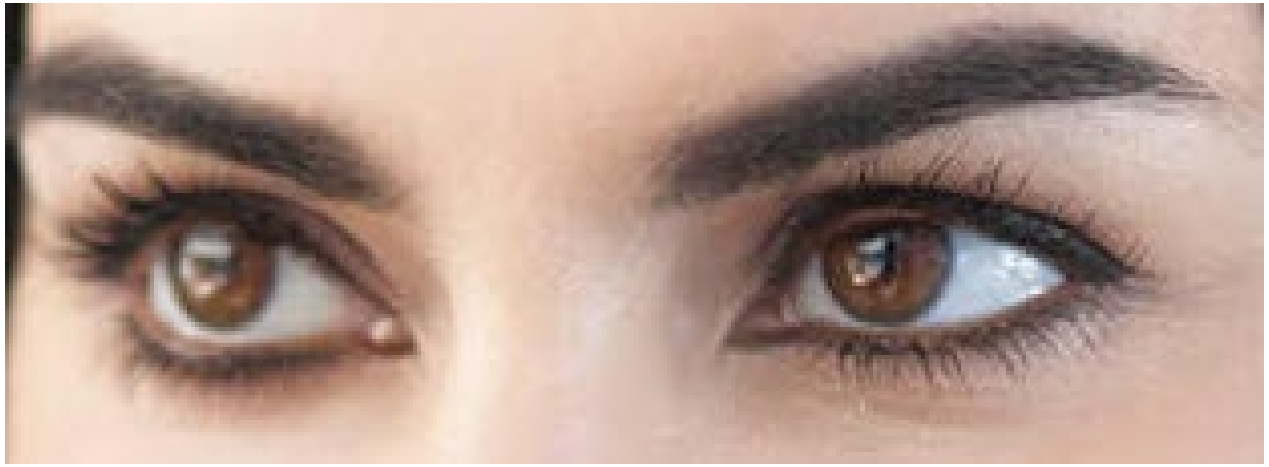
EN ISO 14971:2019+A11:2021

***EN Annexes for the EU were decoupled once Harmonized with EU MDR**
ISO 14971:2019 = EN ISO 14971:2019 Now
EN ISO 14971:2019+A11:2021 is the EU MDR Harmonized Version Now

ISO 14971:2019 – Through the Eyes of a Regulator

1. *Set clear expectations*
2. *Ask open-ended questions*
3. *Review the objective evidence*
4. *Assess and analyze the evidence*

An Excel Spreadsheet Will Be Provided as a Tool With Cases Being Reviewed During the Workshop



How can I leverage ISO 14971:2019 to ensure medical devices are de-risked?

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An Excel Spreadsheet Will Be Provided as a Tool (10 Clauses and Sub-Clauses) With Cases Being Reviewed During the Workshop

Audit Criteria	Open-Ended Questions	Sources of Evidence
4 General requirements for risk management system **4.1 Risk management process** The manufacturer **shall** establish, implement, document, and maintain an ongoing process for: a) identifying hazards and hazardous situations associated with a medical device; b) estimating and evaluating the associated risks; c) controlling these risks, and d) monitoring the effectiveness of the risk control measures. This process **shall** apply throughout the life cycle of the medical device. This process **shall** include the following elements: — risk analysis; — risk evaluation; — risk control; and — production and post-production activities. Where a documented product realization process exists, it **shall** incorporate the appropriate parts of the risk management process. NOTE 1 Product realization processes are described in, for example, Clause 7 of ISO 13485:2016[5]. NOTE 2 A documented process within a quality management system can be used to address safety in a systematic manner, in particular to enable the early identification of hazards and hazardous situations in complex medical devices. NOTE 3 A schematic representation of the risk management process is shown in Figure 1. Depending on the specific life cycle phase, individual elements of risk management can have varying emphasis. Also, risk management activities can be performed iteratively or in multiple steps as appropriate to the medical device. Annex B contains a more detailed overview of the steps in the risk management process. Compliance is checked by inspection of the appropriate documents. SEE FIGURE 1 A schematic representation of the risk mgmt process.	are identified throughout the entire lifecycle of the medical device? 2. Describe the process your organization uses to evaluate and control the risks associated with the identified hazards. 3. How do you integrate the risk management process with your product realization processes, and how is this documented? 4. What mechanisms are in place to monitor the effectiveness of risk control measures during production and post-production activities? 5. Provide examples of how risk management activities are revisited or iteratively applied during different phases of the medical device lifecycle. **LINKAGE QUESTIONS: [For training or to further interrogate Manufacturer)** 1. Linking Clause 4.1 (Risk Management Process) to Clause 4.2 (Competence of Personnel): Question: "How does your organization's risk management process ensure that the personnel involved are competent and have the necessary qualifications to identify and assess risks? Provide examples where personnel competence directly influenced risk identification or mitigation?" 2. Linking Clause 4.1 (Risk Management Process) to Clause 5.2 (Intended Use and Reasonably Foreseeable Misuse): Question: "In what ways does your risk management process account for reasonably foreseeable misuse of the device? How are these considerations integrated into the risk analysis and mitigation strategies?" 3. Linking Clause 4.1 (Risk Management Process) to Clause 5.3 (Identification of Characteristics Related to Safety): Question: "How does the risk management process ensure that all safety-related characteristics of the device are identified and evaluated? Can you describe how these characteristics influence the overall risk assessment?"	1. Risk Management Plan: A documented plan outlining how risk management activities are planned and conducted throughout the lifecycle of the device. 2. Hazard Analysis Reports: Documentation of identified hazards, hazardous situations, and associated risks. 3. Risk Evaluation Documents: Evidence of risk estimation, evaluation, and decision-making processes for accepting or mitigating risks. 4. Risk Control Measures Documentation: Records showing the implementation and effectiveness of risk control measures. 5. Product Realization Process Documentation: Evidence that the risk management process is integrated into the product realization process, such as design and development records, verification, and validation plans. 6. Post-Production Monitoring Reports: Reports or data showing the monitoring of risk control measures during the production and post-production phases. 7. Change Management Records: Documentation of changes made to the medical device or its processes, including re-evaluation of risks. 8. Management Review Minutes: Records of management reviews that include discussions and decisions on risk management activities and the effectiveness of the risk management process.

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ISO 14971:2019 Medical Devices
Application of Risk Management to Medical Devices

BS EN ISO 14971:2019 + A11:2021 (Harmonized to EU MDR) and ISO/TR 24971:2020 (2nd Edition)

4.0 General Requirements for Risk Management System

START HERE

- 4.1 Risk Management Process
- 4.2 Management Responsibilities
- 4.3 Competency of Personnel
- 4.4 Risk Management Plan
- 4.5 Risk Management File

5.0 Risk Analysis

- 5.1 Risk Analysis Process
- 5.2 Intended Use and Reasonably Foreseeable Misuse
- 5.3 Identification of Characteristics Related to Safety
- 5.4 Identification of Hazards and Hazardous Situations
- 5.5 Risk Estimation

6.0 Risk Evaluation

7.0 Risk Control

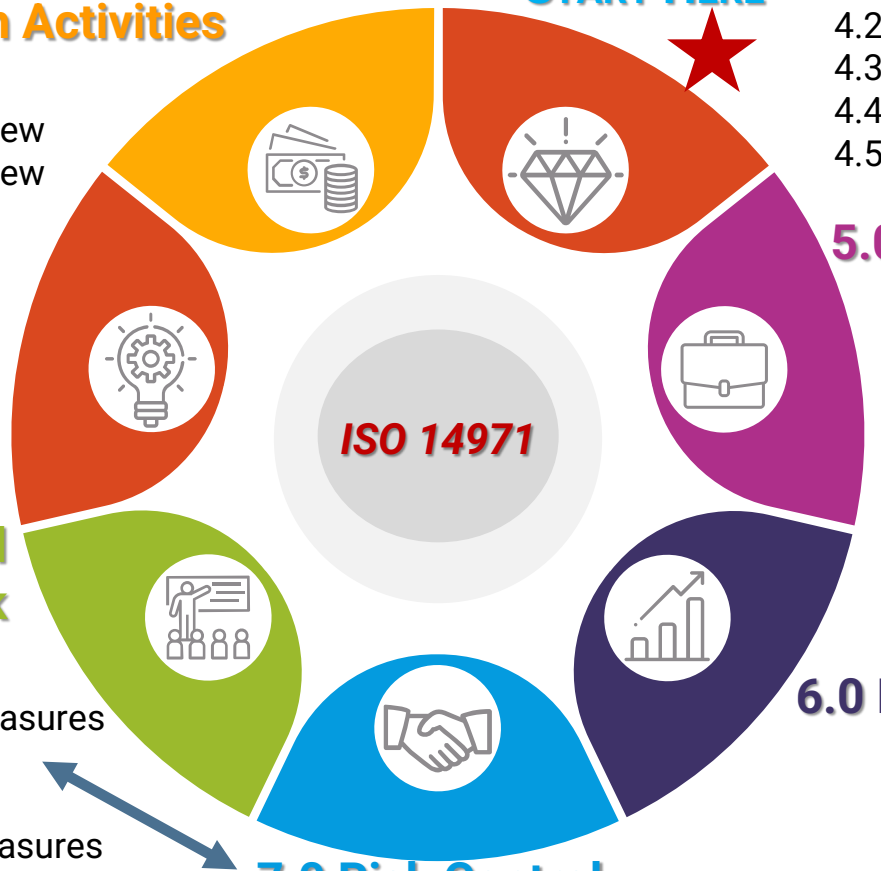
- 7.1 Risk Control Option Analysis
- 7.2 Implementation of Risk Control Measures
- 7.3 Residual Risk Evaluation
- 7.4 Benefit-Risk Analysis
- 7.5 Risks Arising from Risk Control Measures
- 7.6 Completeness of Risk Control

8.0 Evaluation of Overall Residual Risk

9.0 Risk Management Review

10. Production and Post-Production Activities

- 10.1 General
- 10.2 Information Review
- 10.3 Information Review
- 10.4 Actions



ISO 14971:2019 Article 4
Risk Control

- 4.1 Risk Management Process
- 4.2 Management Responsibilities
- 4.3 Competence of Personnel
- 4.4 Risk Management Plan
- 4.5 Risk Management File

ISO 14971:2019 Article 4
General Requirements for Risk Management Systems

TECHNICAL REPORT

ISO/TR 24971

Second edition
2020-06

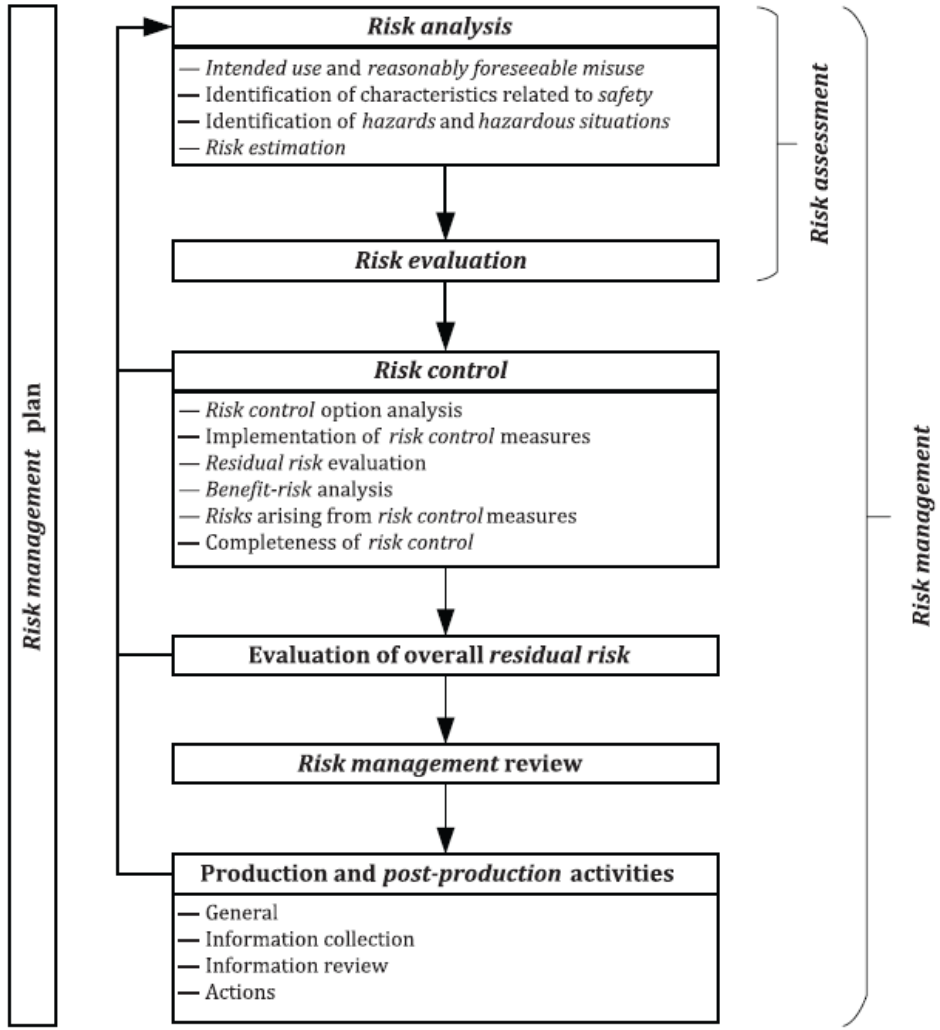


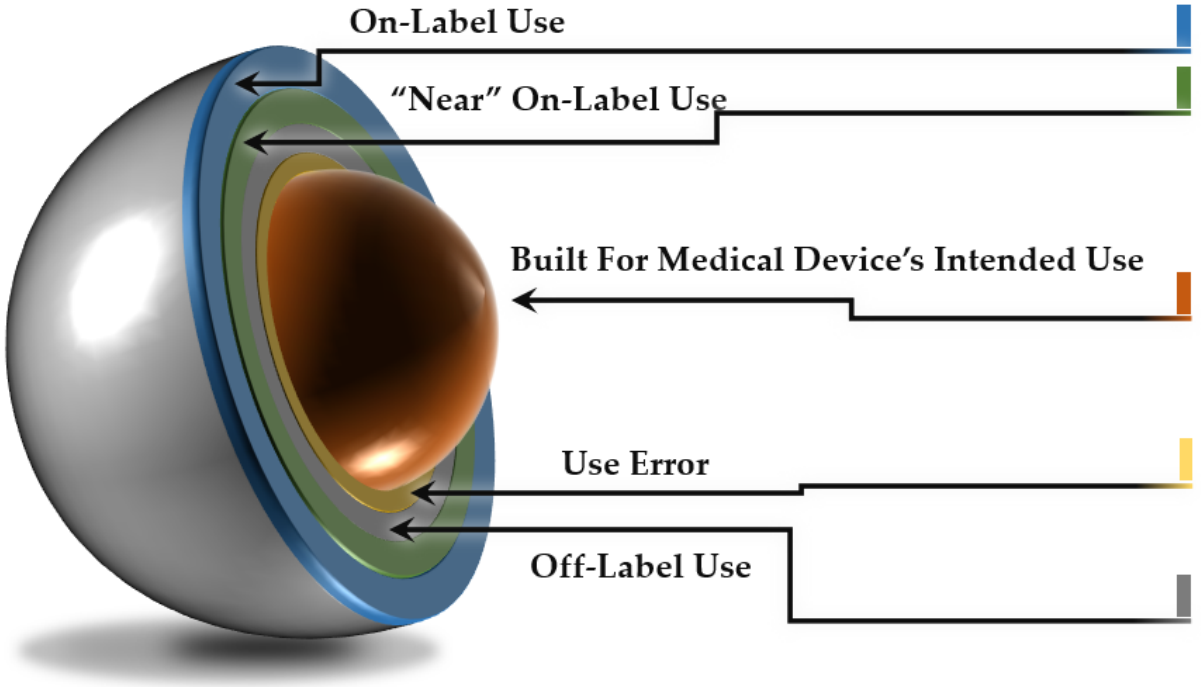
Figure 1 — A schematic representation of the *risk management process*

Identify:
Hazards
Hazardous Situation
Harms
Risks
Implement Controls
Monitor Effectiveness

ISO 14971:2019 Article 4 General Requirements 4.1 Risk Management Process

✓ **Implementing a Structured (Systematic) Risk Management Process (Clause 4.1)**

- **Practical Insight**: By **mandating** that manufacturers **follow** a **structured** process outlined in Clause 4.1, smaller **regulators** can **ensure** that risks are (i) identified, (ii) evaluated, and (iii) controlled consistently throughout the product lifecycle. This process helps **prevent oversight** and **encourages** a **proactive** approach to risk management.
- **1. Empowerment Strategy**: This can **require** detailed documentation of each step in the risk management process, **allowing** for **thorough audits (See EXCEL) and easier identification** of potential **gaps** in manufacturers' risk management systems.



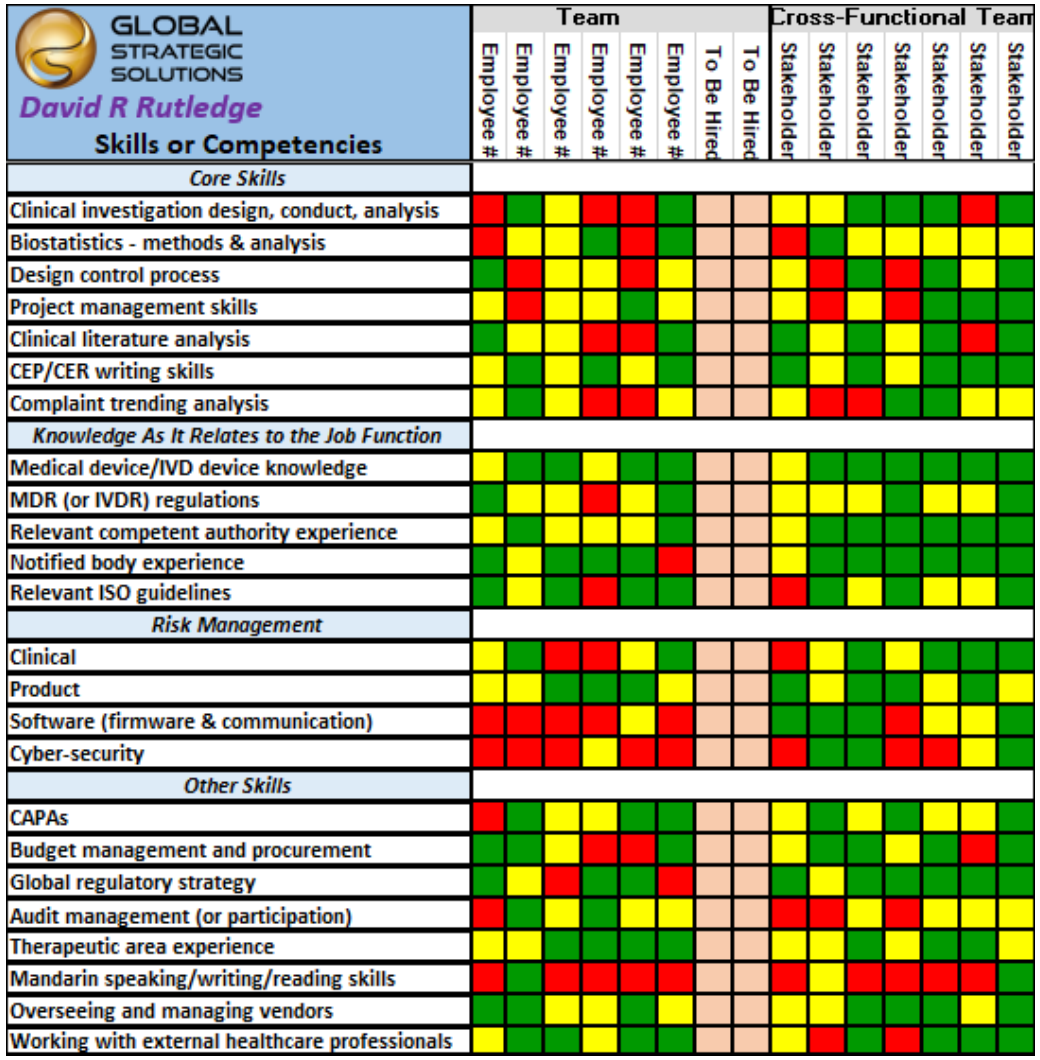
This, in part, is the reason for developing robust risk management systems in your quality management system.

ISO 14971:2019 Article 4 General Requirements
4.2 Management Responsibilities

- ✓ **Ensuring Strong Management Responsibilities (Clause 4.2)**
  - **Practical Insight**: Clause 4.2 highlights the critical role of **management** in risk management activities. Regulators can insist that manufacturers **demonstrate** management's commitment by (i) reviewing their risk management activities, (ii) providing necessary resources, and (iii) fostering a risk-aware culture.
  - **2. Empowerment Strategy**: Smaller regulators can request **regular reports or audits** showing management's active involvement, ensuring that risk management is **not just** a checkbox exercise but a **core component** of the organization's **strategy**.

ISO 14971:2019 Article 4 General Requirements
4.3 Competence of Personnel

- ✓ **Focusing on Competency of Personnel (Clause 4.3)**
  - ➢ **Practical Insight: Ensuring** that personnel involved in risk management are **competent** is crucial for the effectiveness of the process. Regulators can **encourage** manufacturers to invest in **training** and **development** to maintain a high level of expertise among their staff.
  - ➢ **3. Empowerment Strategy: Develop** or **endorse** specific training programs or certifications in **risk management**, making it easier for manufacturers to comply with this requirement and ensuring consistency across the industry.



ISO 14971:2019 Article 4 General Requirements 4.4 Risk Management Plan

- ✓ **Developing and Monitoring a Risk Management Plan (Clause 4.4)**
  - **Practical Insight:** The risk management plan is a dynamic document that outlines the risk management activities for a medical device. Regulators can require that this plan is continuously updated and reflects the current understanding of the device's risks.
  - **4. Empowerment Strategy:** Smaller regulators can review risk management plans as part of the device approval process and mandate periodic updates to the plan, ensuring that it evolves with the product and any new risks identified.

ISO 14971:2019 Article 4 General Requirements 4.5 Risk Management File

- ✓ **Maintaining a Comprehensive Risk Management File (Clause 4.5)**
  - **Practical Insight:** The risk management file serves as a repository for all documents and records related to the risk management process. Regulators can use this file as a primary source of evidence during audits or inspections to assess compliance.
  - **5. Empowerment Strategy:** Smaller regulatory bodies can standardize the format or content of the risk management file to streamline the review process and make it easier to identify key information, ensuring that even with limited resources, they can effectively assess the manufacturer's risk management practices.

ISO 14971:2019 Article 5
Risk Analysis

- 5.1 Risk Analysis Process
- 5.2 Intended Use and Reasonably Foreseeable Misuse
- 5.3 Identification of Characteristics Related Safety
- 5.4 Identification of Hazards and Hazardous Situations
- 5.5 Risk Estimation

ISO 14971:2019 Article 5 Risk Analysis
5.1 Risk Analysis Process

- ✓ **Establishing a Rigorous Risk Analysis Process (Clause 5.1)**
  - **Practical Insight:** Clause 5.1 emphasizes the need for a thorough and systematic risk analysis process. Regulators can require manufacturers to follow a detailed and transparent risk analysis process, ensuring that all potential risks are identified and assessed before the device is marketed.
  - **6. Empowerment Strategy:** Smaller regulatory bodies can develop a checklist or template that manufacturers must complete during the risk analysis phase, ensuring consistency and comprehensiveness in the identification and evaluation of risks.

ISO 14971:2019 Article 5 Risk Analysis
5.2 Intended Use and Reasonably Foreseeable Misuse

- ✓ **Assessing Intended Use and Reasonably Foreseeable Misuse (Clause 5.2)**
  - **Practical Insight:** Understanding the intended use and potential misuse of a device is critical in anticipating how risks might manifest in real-world scenarios. Regulators can require manufacturers to clearly define and document both the intended use and any foreseeable misuse of the device, including how these scenarios were considered during risk analysis.
  - **7. Empowerment Strategy:** Smaller regulators can request case studies or examples from manufacturers showing how similar devices have been misused in the past, using this information to assess the thoroughness of the risk analysis. This helps smaller regulatory bodies leverage existing data to ensure comprehensive risk assessment.

ISO 14971:2019 Article 5 Risk Analysis
5.3 Identification of Characteristics Related to Safety

✓ **Identifying Characteristics Related to Safety (Clause 5.3)**

- **Practical Insight:** Clause 5.3 focuses on identifying specific characteristics of the device that are related to safety. Regulators can require manufacturers to list these characteristics explicitly and explain how each one was addressed in the risk management process.
- **8. Empowerment Strategy:** Smaller regulatory bodies can develop guidelines or tools to help manufacturers systematically identify safety-related characteristics, ensuring that even those with limited experience can thoroughly evaluate the device's safety features.

ISO 14971:2019 Article 5 Risk Analysis
5.4 Identification of Hazards and Hazards Situations

✓ **Identifying Characteristics Related to Safety (Clause 5.4)**

- **Practical Insight:** Identifying all possible hazards and hazardous situations is a key step in preventing harm. Regulators can require manufacturers to conduct comprehensive hazard identification, ensuring that all potential sources of harm are considered, including those that may be less obvious.
- **9. Empowerment Strategy:** Smaller regulators can encourage or mandate the use of specific hazard identification techniques (e.g., Failure Modes and Effects Analysis, or Fault Tree Analysis) to ensure thoroughness. This can be particularly useful for smaller regulatory bodies that may not have the resources to develop their own hazard identification frameworks.

Medical device	*Hazard*	*Hazardous situation*	Inherently safe design	Protective measure	Information for *safety*
Syringe (for single use)	Biological contamination	Reuse after previous use on another patient	Self-destruction after use	Clear indication of first use	Warning against reuse
Implantable pacemaker	Loss of functionality	Pacemaker stops functioning due to early battery depletion	Reliable long-life batteries	Alarm before battery depletion	Information on typical battery lifetime
Mechanical patient ventilator	Air pressure	Software failure causes excessive pressure in patient airway	Blower incapable of delivering high pressure	Over-pressure valve in ventilator or in breathing hose	Instruction to use only breathing hose delivered by *manufacturer*
IVD blood analyser	Systematic error or bias	Incorrect result reported to clinician	Self-calibration	Metrologically traceable calibrators provided	Instruction to verify calibration with trueness controls
X-ray equipment	Ionising radiation	Staff exposed to stray radiation	Not feasible (stray radiation always occurs)	Lead shields and lead aprons	Information on radiation level in occupancy zones

ISO 14971:2019 Article 5 Risk Analysis
5.5 Risk Estimation

- ✓ **Ensuring Accurate Risk Estimation (Clause 5.5)**
  - **Practical Insight:** Risk estimation involves evaluating the probability and severity of harm for each identified hazard. Regulators can require that manufacturers provide clear and well-documented justifications for their risk estimates, ensuring that these estimates are based on solid data and reasonable assumptions.
  - **10. Empowerment Strategy:** Smaller regulatory bodies can standardize the risk estimation process by providing guidelines on acceptable methods for estimating risk, such as using predefined scales for probability and severity. This approach can help ensure consistency and reliability in risk estimations across different manufacturers.

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ISO 14971:2019
Article 6
Risk Evaluation

ISO 14971:2019 Article 6 Risk Evaluation (Short Clause, but Impactful to Regulators)

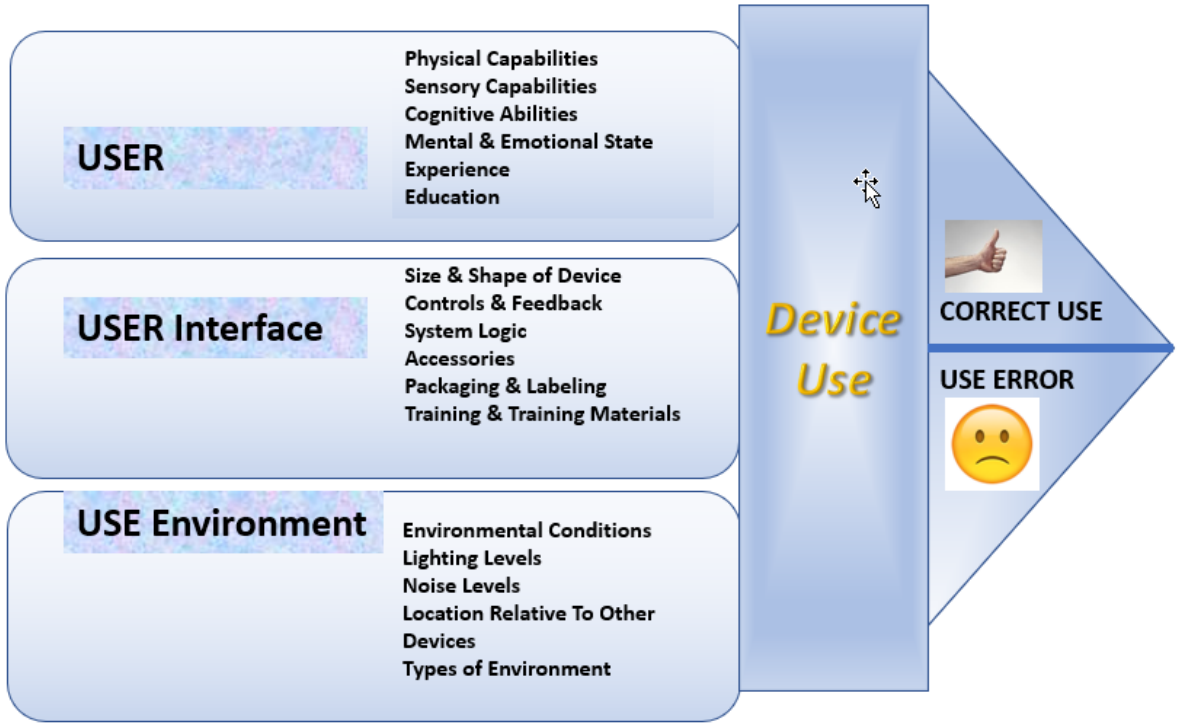
✓ **Reinforcing the Need for Manufacturer-Defined Risk Acceptability Criteria (Clause 6.0)**

- **Practical Insight:** ISO 14971:2019 requires manufacturers to define their criteria for risk acceptability based on their internal policies, as stated in the risk management plan. Regulators can ensure that manufacturers clearly document these criteria, which serve as the benchmark for evaluating whether a risk is acceptable.
- **11. Empowerment Strategy:** Smaller regulatory bodies can develop or endorse guidelines that help manufacturers establish appropriate risk acceptability criteria. This can ensure that even smaller or less experienced manufacturers have a clear understanding of what constitutes an acceptable level of risk tailored to the specific needs of their region.

ISO 14971:2019 Article 6 Risk Evaluation (Short Clause, but Impactful to Regulators)

✓ **Thoroughly Documenting the Risk Evaluation Process (Clause 6.0)**

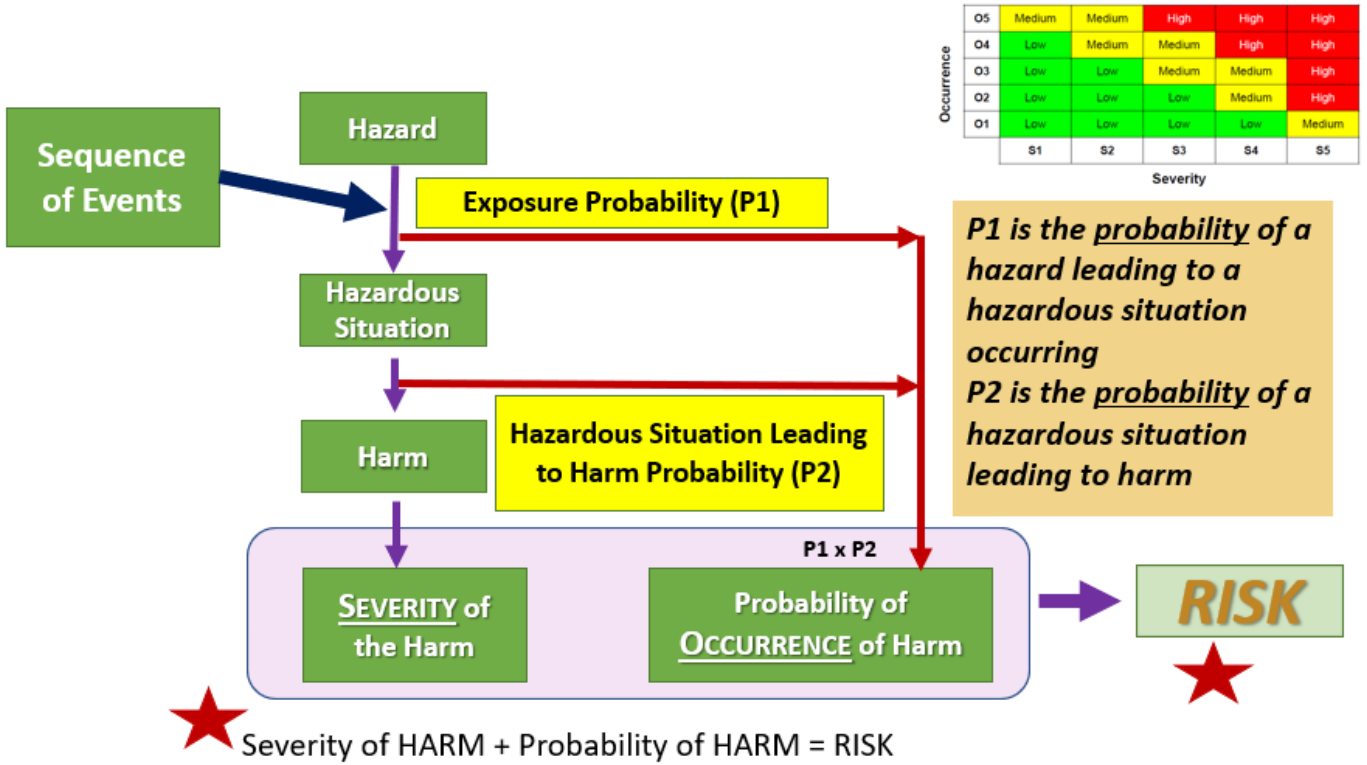
- **Practical Insight:** ISO 14971:2019 emphasizes the importance of documenting the risk evaluation process, including whether the criteria for risk acceptability have been met. Regulators can require manufacturers to maintain comprehensive records of this evaluation, ensuring that the decision-making process is transparent and traceable.
- **12. Empowerment Strategy:** Smaller regulatory bodies can provide a standardized template or checklist for documenting risk evaluations. This ensures that manufacturers consistently and thoroughly record their risk evaluations, making it easier for regulators to review and understand the basis for the manufacturer's decisions.



ISO 14971:2019 Article 6 Risk Evaluation (Short Clause, but Impactful to Regulators)

✓ **Leveraging Annex C for Enhanced Understanding and Consistency (Clause 6.0)**

- **Practical Insight:** Annex C of ISO 14971:2019 provides additional guidance and examples on applying risk acceptability criteria during risk evaluation. Regulators can encourage manufacturers to refer to this annex when conducting their risk evaluations to ensure a consistent and well-understood approach to assessing risk acceptability.
- **13. Empowerment Strategy:** Smaller regulatory bodies can highlight key points from Annex C in their regulatory guidelines or training programs, helping manufacturers and regulators alike to apply a consistent and robust approach to risk evaluation.



ISO 14971:2019 Article 7
Risk Control

- 7.1 Risk Control Option Analysis
- 7.2 Implementation of Risk Control Measures
- 7.3 Residual Risk Evaluation
- 7.4 Benefit-Risk Analysis
- 7.5 Risks Arising from Risk Control Measures
- 7.6 Completeness of Risk Control

ISO 14971:2019 Article 7 Risk Control 7.1 to 7.6

Hazard traceability matrix (Risk analysis)

Potential Source of the Harm (3.4)	Circumstance in which people, Property, or the Environment is/are Exposed to One or More Hazards (3.5)	Injury or Damage to the Health of People, Or Damage to Property, or Environment (3.3)	Combination of the Probability of Occurrence of Harm and the Severity of that Harm (3.18)
Hazard	**Hazardous Situation**	**Harm**	**Risk** (occurrence & severity of harm)

	Risk analysis							Risk eval.	Risk control									
ID	Hazard	Reasonably forseeable sequence or combination of events	Hazardous situation	Harm	Notes	Probability (Po)	Severity	Acceptable?	Risk control options and rationale Clause 7.1	Risk control measure Clause 7.2	Risk control verification Clause 7.2	Implemented? (Clause 7.1, 7.2)	F/Up -Po Clause 7.2	F/Up -Severity Clause 7.2	Residual risk Clause 7.3	Residual risk	Has the risk been reduced AFAP?	Benefit-Risk Analysis Clause 7.4
1	Light					1	3	ACC					1	4		ACC*		
2	Temperature					3	4	N ACC					1	5		ACC*		
3	Microbiology: Bacteria, Virus, Fungas					1	5	ACC*					4	3	12	N ACC		
4	Electrical Outlet							TBD							0	TBD		
5	Production Residues							TBD								TBD		

Terminology of Risk Management

Hazard	Potential source of harm (**Nothing bad has happened yet**.) If someone was exposed to this thing could they potentially be harmed? Yes, then hazard. Loss of therapy. Wrong therapy. Not dead battery – that is a cause of a hazard.
Hazardous Situation	Circumstance in which people, property, or the environment are exposed to one or more hazard(s) (**A situation where Harm could occur**). Is there a hazard present and is there exposure? You have to have both. Use a phrase that describes exposure to hazard(s)
Foreseeable Events	Something that could occur due to design issues, manufacturing issues, user misuse. Events that could lead to the patient being exposed to the hazard and being harmed.
Harm	Injury or damage to the health of people, or damage to property or the environment (**Physical Injury must have occurred**) Was something done to somebody or something? Describe an injury. Burn or infection. Death is not a harm, but a potential consequence of a harm.
Risk	Combination of the probability of **occurrence** of harm and the **severity** of that harm (**These two elements are needed to be classified as a risk**) "The objectified uncertainty regarding the occurrence of an undesirable event" – Willett 1901 (Probability of sustaining harm in a hazardous situation.)
Risk Analysis	**Systematic** use of available information to identify hazards and to estimate the risk
Risk Estimation	Process used to assign **values** to the probability of occurrence of harm and the severity of that harm. Add numbers. What is the probability?
Risk Evaluation	Process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk. You have to have risk acceptance criteria.
Risk Control	Process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels
State-of-the-Art	What is currently and generally accepted as good practice ***After controls are in place, there should be a continuous evaluation of risk***

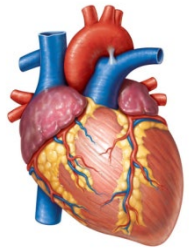
Classify: Hazard Hazardous Situation Harm Risk (occurrence and severity of harm)

Source of the harm

Physical Injury

Distinctions – Quiz (Refer to Previous Definitions)

1) High voltage in mains power outlets
2) A person touching a live household wire
3) Electrocution resulting in death 0.5% of time
4) Snake venom
5) Snake venom in blood stream
6) A defective cardiac stent in its package
7) A broken cardiac stent that is implanted in a patient
8) A 1% chance of a perforated coronary artery causing death
9) A contaminated batch of a device or drug
10) Ingested contaminated drug or implanted contaminated device



Group Activity During Talk

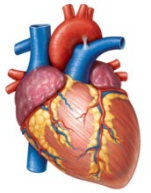
Distinctions - Quiz

Classify:

Hazard Hazardous Situation Harm Risk (occurrence & severity of harm)

Source of the harm Physical Injury

1) High voltage in mains power outlets – Hazard
2) A person touching a live household wire – Hazardous Situation
3) Electrocution resulting in death 0.5% of the time – Risk
4) Snake venom – Hazard
5) Snake venom in blood stream – Hazardous Situation
6) A defective device product in its package – Hazard
7) A broken medical device that is implanted in a patient – Hazard Situation
8) A 1% chance of a perforated coronary artery, septum, or valve causing death – Risk
9) A contaminated batch of a medical device – Hazard
10) Implanted contaminated device – Hazardous Situation

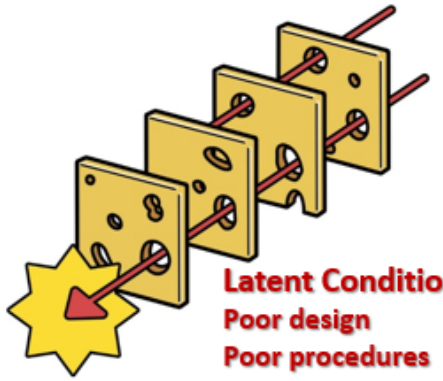


ISO 14971:2019 Risk Control

Swiss Cheese Model of Preventing Adverse Events (James Reason and Dante Orlandella)

Cheese Slices*: *Examples of Controls

1. **Creating** a **user interface** that reflects good human factors engineering
2. **Safeguards** to prevent exposure to hazards that cannot be removed
3. **Warnings** to alert users to take precautions, e.g., bells, beeps, lights
4. **IFUs** – Instructions to guide safe interactions
5. **Trainings** and then checking the effects of training



Patient Safety Incident

Latent Conditions:
Poor design
Poor procedures
Poor Mgmt. decisions

Cheese Slice – represents multiple efforts or defenses to prevent an accident or adverse event from a device

EU Harmonized Standard, EN ISO 14971:2019/A11:2021

1. Inherently safe design
2. Protective measures – in device or during manufacturing
3. Information for safety – labeling and IFU

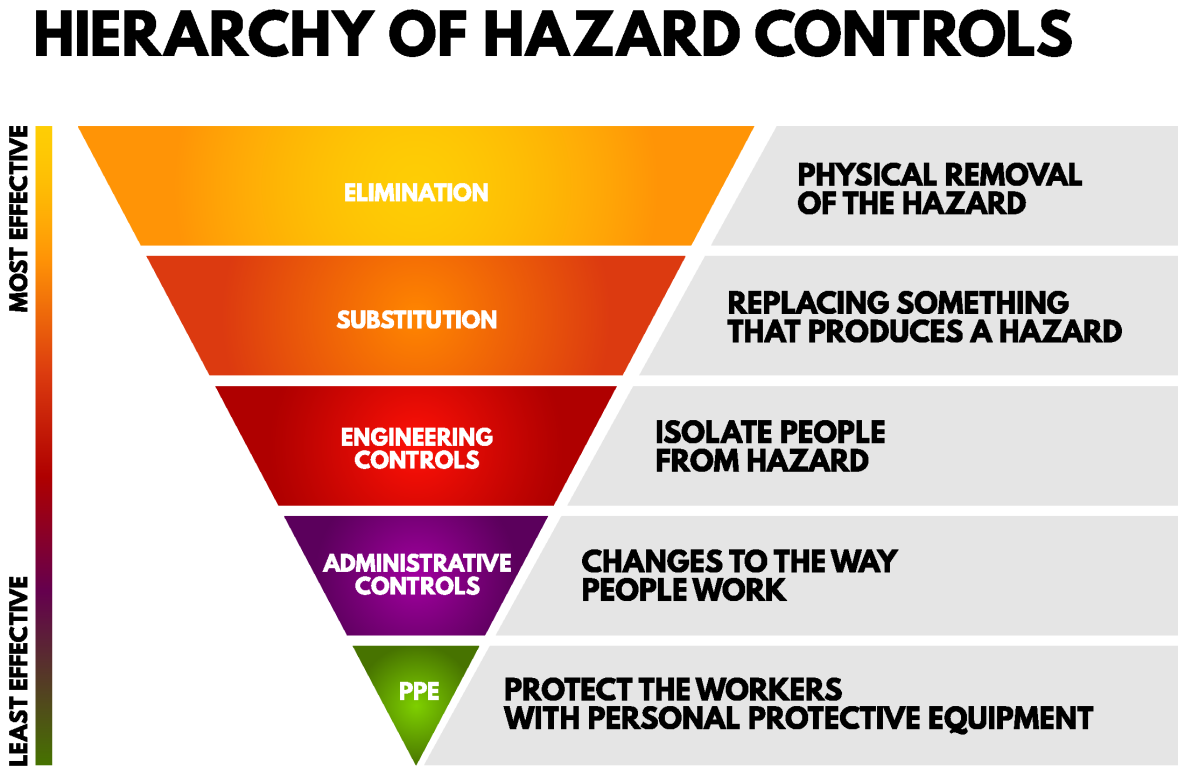
ISO 14971:2019 Article 7 Risk Control
7.1 Risk Control Option Analysis

- ✓ **Risk Control Option Analysis (Clause 7.1)**
  - **Practical Insight:** ISO 14971:2019 requires manufacturers to identify and evaluate different risk control options to reduce risks to acceptable levels. Regulators can require manufacturers to document and justify the selection of risk control measures, ensuring that the most effective and feasible options are chosen.
  - **14. Empowerment Strategy:** Smaller regulatory bodies can provide guidance on common risk control strategies (e.g., inherent safety by design, protective measures, or information for safety) and require manufacturers to consider these strategies in their analysis. This approach helps ensure that all potential risk control options are explored and that the most appropriate ones are implemented.

ISO 14971:2019 Article 7 Risk Control
7.2 Implementation of Risk Control Measures

✓ **Implementation of Risk Control Measures (Clause 7.2)**

- **Practical Insight:** Once risk control measures are selected, ISO 14971:2019 mandates that they be implemented and verified for effectiveness. Regulators can require manufacturers to provide evidence of the successful implementation and verification of these measures, ensuring that the controls are not only planned but also effectively executed.
- **15. Empowerment Strategy:** Smaller regulatory bodies can provide guidance on common risk control strategies (e.g., inherent safety by design, protective measures, or information for safety) and require manufacturers to consider these strategies in their analysis. This approach helps ensure that all potential risk control options are explored and that the most appropriate ones are implemented.



ISO 14971:2019 Article 7 Risk Control
7.3 Residual Risk Evaluation

✓ **Residual Risk Evaluation (Clause 7.3)**

- **Practical Insight:** After implementing risk control measures, manufacturers must evaluate any remaining (residual) risks. ISO 14971:2019 requires that these residual risks be compared to the **predefined** risk acceptability criteria. Regulators can ensure that manufacturers provide a clear and documented evaluation of residual risks, including an assessment of whether these risks are acceptable.
- **16. Empowerment Strategy:** Smaller regulatory bodies can develop standardized tools or templates for residual risk evaluation, making it easier for manufacturers to document and regulators to assess the remaining risks. This helps ensure that residual risks are properly evaluated and managed.

ISO 14971:2019 Article 7 Risk Control
7.4 Benefit-Risk Evaluation

- ✓ **Benefit-Risk Analysis (Clause 7.4)**
  - **Practical Insight:** In cases where residual risks exceed the predefined acceptability criteria, ISO 14971:2019 requires a benefit-risk analysis to determine if the benefits of the device outweigh the residual risks. Regulators can require manufacturers to conduct and document a thorough benefit-risk analysis, particularly for high-risk devices.
  - **17. Empowerment Strategy:** Smaller regulatory bodies can provide guidelines on conducting benefit-risk analyses, including examples of factors to consider (e.g., clinical benefits, severity of the disease, availability of alternative treatments). This helps ensure that benefit-risk decisions are well-founded and transparent.

ISO 14971:2019 Article 7 Risk Control
7.5 Risks Arising from Risk Control Measures

- ✓ **Risks Arising from Risk Control Measures (Clause 7.5)**
  - **Practical Insight:** Implementing risk control measures can sometimes **introduce** new risks. ISO 14971:2019 requires manufacturers to identify and evaluate any new risks that arise from the implementation of risk controls. Regulators can ensure that manufacturers document these new risks and assess their impact on the overall risk profile of the device.
  - **18. Empowerment Strategy:** Smaller regulatory bodies can require manufacturers to update their risk management files with any new risks identified during the implementation of risk control measures. This ensures that all risks, including those introduced by the controls themselves, are identified and managed appropriately.

ISO 14971:2019 Article 7 Risk Control
7.6 Risks Completeness of Risk Control

- ✓ **Completeness of Risk Control (Clause 7.6)**
  - ➢ **Practical Insight:** ISO 14971:2019 mandates that manufacturers assess the completeness of their risk control measures to ensure that all identified risks have been addressed. Regulators can require manufacturers to provide a summary report or a checklist confirming that all risks have been controlled to the extent possible.
  - ➢ **19. Empowerment Strategy:** Smaller regulatory bodies can develop or recommend a standardized checklist for assessing the completeness of risk control measures. This tool can help manufacturers systematically verify that all identified risks have been addressed and provide regulators with a clear overview of the risk control process.

Hazard	Foreseeable sequence of events	*Hazardous situation*	*Harm*
Electromagnetic energy (high voltage)	(1) Electrode cable unintentionally plugged into power line receptacle	Line voltage appears on electrodes	Serious burns Heart fibrillation
Chemical (volatile solvent, embolus)	(1) Incomplete removal of volatile solvent used in manufacturing (2) Solvent residue converts to gas at body temperature	Development of gas embolism (bubbles in the blood stream) during dialysis	Infarct Brain damage
Biological (microbial contamination)	(1) Inadequate instructions provided for decontaminating re-used anaesthesia tubing (2) Contaminated tubing used during anaesthesia	Bacteria released into airway of patient during anaesthesia	Bacterial infection
Functionality (no delivery)	(1) Electrostatically charged patient touches infusion pump (2) Electrostatic discharge (ESD) causes pump and pump alarms to fail	Failure to deliver insulin to patient with elevated blood glucose level, no warning given	Minor organ damage Decreased consciousness
Functionality (no output)	(1) Implantable defibrillator battery reaches the end of its useful life (2) Inappropriately long interval between clinical follow-up visits	Defibrillator cannot deliver shock when an arrhythmia occurs	Death
Measurement (incorrect information)	(1) Measurement error (2) No detection by user	Incorrect information reported to clinician, leading to misdiagnosis and/or lack of proper therapy	Progression of disease Serious injury

ISO 14971:2019 Article 8 Evaluation of Overall Residual Risk

ISO 14971:2019 Article 8.0 Evaluation of Overall Residual Risk Another Small Clause with Huge Implications

- ✓ **Requiring a Comprehensive Evaluation of Overall Residual Risk (Clause 8.0)**
  - **Practical Insight:** ISO 14971:2019 mandates that manufacturers evaluate the overall residual risk after implementing all risk control measures, considering all residual risks collectively. Regulators can require manufacturers to provide a detailed and documented assessment of the overall residual risk, ensuring that this evaluation is thorough and considers the cumulative impact of all identified risks.
  - **20. Empowerment Strategy:** Smaller regulatory bodies can request that manufacturers use a structured approach, such as a risk matrix or other quantitative methods, to evaluate the overall residual risk. This helps ensure consistency in the evaluation process and makes it easier for regulators to review and understand the manufacturer's decision-making.

ISO 14971:2019 Article 8.0 Evaluation of Overall Residual Risk Another Small Clause with Huge Implications

✓ **Ensuring the Use of Predefined Acceptability Criteria (Clause 8.0)**

- **Practical Insight:** The evaluation of overall residual risk must be done using the criteria for acceptability defined in the risk management plan. Regulators can ensure that these criteria are clearly documented and were applied appropriately during the evaluation process.
- **21. Empowerment Strategy:** Smaller regulatory bodies can develop or endorse predefined risk acceptability criteria specific to their region or the types of devices being regulated. This approach helps standardize the evaluation process and ensures that all manufacturers are held to the same standards of risk acceptability.

For each hazard, the severity is estimated from literature, user feedback, similar products, guidelines, FDA Medical Device Reports, MAUDE, eventually EUDAMED, etc.

All potential causes are listed and for each cause the likelihood of occurrence is estimated using number of devices shipped, literature, user feedback, complaints, device returns, etc.

A risk level is determined and judged for acceptability. If it is not yet acceptable, countermeasures are defined.

ISO 14971:2019 Article 8.0 Evaluation of Overall Residual Risk
Another Small Clause with Huge Implications

✓ **Mandating Disclosure of Significant Residual Risks (Clause 8.0)**

- **Practical Insight:** If the overall residual risk is deemed acceptable, ISO 14971:2019 requires that significant residual risks be disclosed to users. Regulators can require manufacturers to provide clear, accessible information about these risks in the device's accompanying documentation, ensuring that users are fully informed of any potential dangers.
- **22. Empowerment Strategy:** Smaller regulatory bodies can provide guidelines or templates for disclosing significant residual risks. This ensures that the information is communicated effectively and consistently, making it easier for users to understand the risks associated with the device.

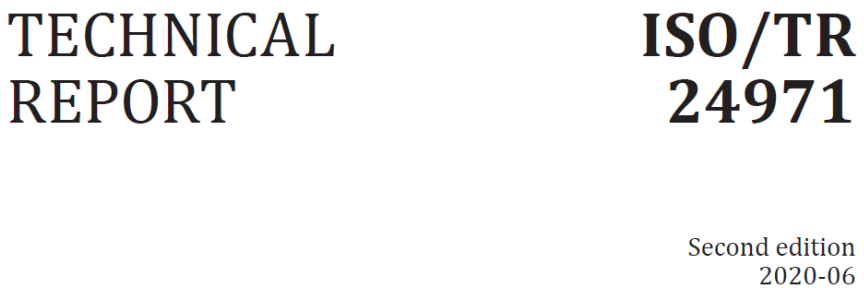
ISO 14971:2019 Article 8.0 Evaluation of Overall Residual Risk Another Small Clause with Huge Implications

- ✓ **Requiring Thorough Documentation and Inspection (Clause 8.0)**
  - **Practical Insight:** The results of the overall residual risk evaluation must be recorded in the risk management file, and regulators are responsible for inspecting this documentation. Smaller regulatory bodies can ensure that manufacturers maintain comprehensive records of their risk evaluations and make these documents readily available for inspection.
  - **23. Empowerment Strategy:** Smaller regulatory bodies can use standardized inspection checklists to ensure that all necessary documentation is present and that the overall residual risk evaluation has been conducted according to ISO 14971:2019 requirements. This helps streamline the inspection process and ensures thorough oversight.

ISO 14971:2019 Article 8.0 Evaluation of Overall Residual Risk Another Small Clause with Huge Implications

✓ **Leveraging Guidance from ISO/TR 24971 (Clause 8.0)**

- **Practical Insight:** ISO 14971 references ISO/TR 24971 for additional guidance on evaluating overall residual risk and disclosing residual risks. Regulators can encourage manufacturers to consult this guidance to enhance their risk evaluation processes.
- **24. Empowerment Strategy:** Smaller regulatory bodies can highlight key sections of ISO/TR 24971 in their training programs or regulatory guidelines, providing manufacturers with additional resources to improve their risk management practices and ensuring consistency in how overall residual risk is evaluated and communicated.



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ISO 14971:2019 Article 9 Risk Management Review

ISO 14971:2019 Article 9.0 Risk Management Review

✓ **Ensuring Comprehensive Execution of the Risk Management Plan (Clause 9.0)**

- **Practical Insight:** ISO 14971:2019 mandates that before a medical device is released for commercial distribution, the manufacturer must review the execution of the risk management plan to ensure it has been properly implemented. Regulators can require manufacturers to provide evidence that all aspects of the risk management plan were carried out as intended, including risk analysis, control, and evaluation.
- **25. Empowerment Strategy:** Smaller regulatory bodies can develop a checklist or template that manufacturers must complete to demonstrate that each element of the risk management plan has been addressed. This ensures a thorough review and provides a clear framework for regulators to verify compliance.

ISO 14971:2019 Article 9.0 Risk Management Review

- ✓ **Ensuring Systems are in Place for Production and Postproduction Monitoring (Clause 9.0)**
  - **Practical Insight:** Clause 9.0 requires manufacturers to confirm that appropriate methods are in place to collect and review information during the production and postproduction phases. Regulators can ensure that manufacturers have established robust systems for ongoing monitoring of the device's safety and performance after it enters the market.
  - **26. Empowerment Strategy:** Smaller regulatory bodies can require manufacturers to provide a detailed plan for production and postproduction monitoring, including how data will be collected, analyzed, and used to inform future risk management activities. This ensures that potential risks are continually monitored and managed throughout the product's lifecycle.

ISO 14971:2019 Article 9.0 Risk Management Review

✓ **Requiring a Risk Management Report (Clause 9.0)**

- **Practical Insight:** The results of the risk management review must be documented in a risk management report and included in the risk management file. Regulators can ensure that this report is comprehensive, detailing the implementation of the risk management plan, the evaluation of overall residual risk, and the methods in place for post-market monitoring.
- **27. Empowerment Strategy:** Smaller regulatory bodies can provide a standardized report format or checklist to ensure that manufacturers include all necessary information in the risk management report. This helps regulators quickly verify that the review has been conducted thoroughly and that all required elements have been addressed.

ISO 14971:2019 Article 9.0 Risk Management Review

✓ **Assigning Responsibility for Risk Management Review (Clause 9.0)**

- **Practical Insight:** The responsibility for conducting the risk management review must be assigned to individuals with the appropriate authority, as defined in the risk management plan. Regulators can ensure that the designated individuals have the necessary expertise and authority to conduct a meaningful review.
- **28. Empowerment Strategy:** Smaller regulatory bodies can require manufacturers to provide the credentials of the individuals responsible for the risk management review, ensuring they have the appropriate qualifications and experience. This helps ensure that the review is conducted by competent personnel who can make informed decisions about the device's safety.

ISO 14971:2019 Article 9.0 Risk Management Review

✓ **Inspecting the Risk Management File for Compliance (Clause 9.0)**

- **Practical Insight:** Compliance with Clause 9.0 is verified by inspecting the risk management file, which should include the risk management report and all related documentation. Regulators can conduct detailed inspections of the risk management file to ensure that the manufacturer has adhered to all requirements of the risk management review.
- **29. Empowerment Strategy:** Smaller regulatory bodies can develop a checklist or set of guidelines for inspecting the risk management file, ensuring that all aspects of the risk management review are thoroughly documented and that the file is complete. This approach helps regulators efficiently verify compliance with ISO 14971:2019.

ISO 14971:2019 Article 10
Risk Control

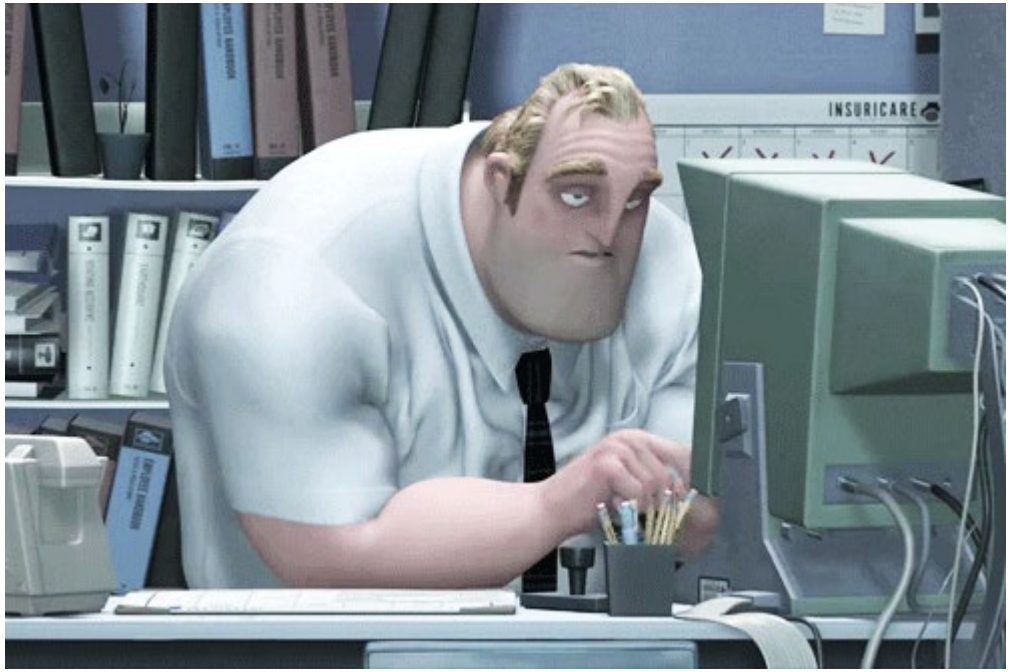
- 10.1 General
- 10.2 Information Collection
- 10.3 Information Review
- 10.4 Actions

ISO 14971:2019 Article 10.0 Production and Post-Production Activities

- ✓ **Ensuring a Comprehensive Approach to Production and Post-Production Risk Management (Clause 10.1 General)**
  - **Practical Insight:** ISO 14971:2019 requires manufacturers to establish and maintain a system for monitoring the safety of the medical device during production and post-production phases. Regulators can ensure that manufacturers have a comprehensive approach to capturing, analyzing, and responding to safety-related data throughout the product's lifecycle.
  - **30. Empowerment Strategy:** Smaller regulatory bodies can develop or endorse guidelines that outline the essential elements of a robust production and post-production monitoring system. This could include mandatory reporting timelines, types of data to be collected, and methods for analyzing and responding to that data. Ensuring that manufacturers follow these guidelines helps maintain the safety and effectiveness of the device after it has been released to the market.

ISO 14971:2019 Article 10.0 Production and Post-Production Activities

- ✓ **Ensuring a Comprehensive Approach to Production and Post-Production Risk Management (Clause 10.2 Information Collection)**
  - **Practical Insight:** Clause 10.2 emphasizes the need for manufacturers to collect and review information about the medical device's performance, including any feedback from users, complaints, and post-market surveillance data. Regulators can ensure that manufacturers have effective systems in place to collect and analyze this information systematically.
  - **31. Empowerment Strategy:** Smaller regulatory bodies can require manufacturers to submit periodic reports detailing the information collected during post-production, including data from clinical use, user feedback, and adverse event reports. By reviewing these reports, regulators can monitor ongoing compliance with safety standards and ensure that manufacturers are responding appropriately to any emerging risks.

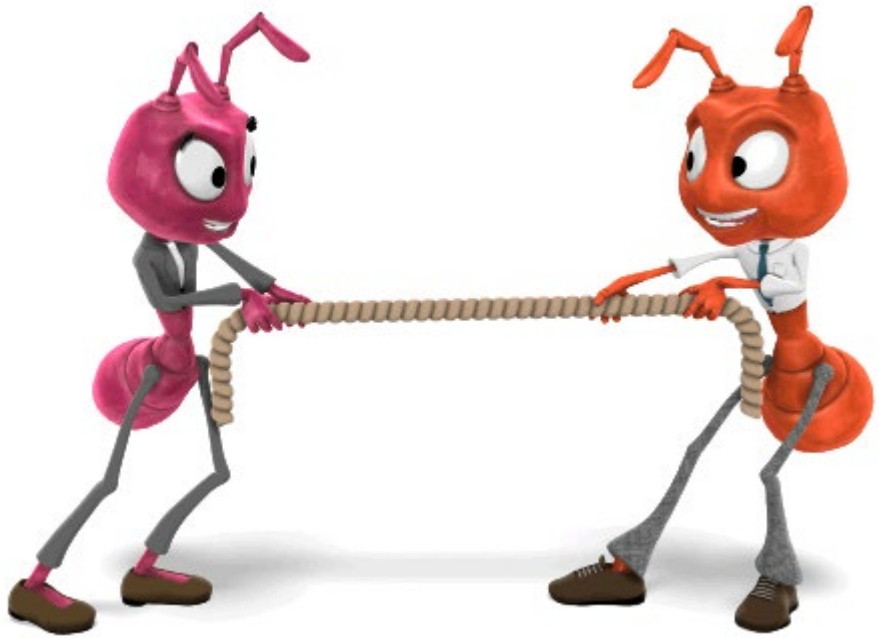


ISO 14971:2019 Article 10.0 Production and Post-Production Activities

- ✓ **Mandating Thorough Information Analysis and Evaluation (Clause 10.3 Information Review)**
  - **Practical Insight:** After collecting information, manufacturers must analyze and evaluate the data to determine if any new risks have emerged or if existing risks have changed. Regulators can require manufacturers to document their analysis processes, ensuring that all collected data is systematically reviewed for potential safety concerns.
  - **32. Empowerment Strategy:** Smaller regulatory bodies can develop or recommend specific analytical methods or tools for manufacturers to use when reviewing post-production information. This can include risk assessment frameworks, trend analysis tools, and root cause analysis techniques. Providing these resources helps manufacturers identify and respond to potential risks effectively.

ISO 14971:2019 Article 10.0 Production and Post-Production Activities

- ✓ **Implementing Corrective and Preventive Actions (Clause 10.4 Actions)**
  - **Practical Insight:** If the review of post-production information reveals new risks or changes in existing risks, manufacturers are required to take appropriate actions, which may include updating the risk management plan, implementing additional risk controls, or modifying the device. Regulators can ensure that manufacturers have a clear process for determining and implementing corrective and preventive actions.
  - **33. Empowerment Strategy:** Smaller regulatory bodies can require manufacturers to submit a corrective and preventive action (CAPA) plan when new risks are identified during post-production. This plan should outline the steps the manufacturer will take to address the risks, including timelines and responsibilities. By reviewing and approving these plans, regulators can ensure that manufacturers take prompt and effective action to maintain the safety of their devices.



ISO 14971:2019 Article 10.0 Production and Post-Production Activities

- ✓ **Ensuring Effective Communication and Documentation (Clause 10 Throughout)**
  - **Practical Insight:** Throughout Clause 10.0, effective communication and thorough documentation are emphasized. Regulators can require manufacturers to maintain detailed records of all production and post-production activities, including the collection, analysis, and response to information. This documentation should be readily available for regulatory review.
  - **34. Empowerment Strategy:** Smaller regulatory bodies can provide a standardized format or checklist for documenting production and post-production activities. This not only helps manufacturers ensure compliance with ISO 14971:2019 but also makes it easier for regulators to review and audit these activities, ensuring that all necessary steps have been taken to manage risks throughout the device's lifecycle.

Risk Management (ISO 14971:2019) December 2019

- **Myth #1 – We don't need a Risk Management Plan because we have an SOP in place**
  - ✓ **At the product level, EVERY product needs a plan.**

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Risk Management (ISO 14971:2019) December 2019

- **Myth #2 – There is no Technical Report that can be used for training purposes**
  - ✓ **Yes, there is.**
  - ✓ **ISO/TR 24971:2020 (June) Second Edition.**

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There is Little Information in ISO 14971 that can Assist Regulators

- **Myth #3 – There is Little Information in ISO 14971 that can Assist Regulators**
  - ✓ **Yes, there is. You have just been shown 34 Empowering Strategies.**
  - ✓ **Plus, the Excel file is another useful tool.**

GLOBAL™ STRATEGIC SOLUTIONS

How Do Quality Standards (ISO 14971:2019 and Application of Risk Management) De-Risk Devices?

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Understanding the Tools for Postmarket Risk Management

September 16, 2024

Bridging Consulting LLC

REGULATORY · QUALITY · CLINICAL

Yu Zhao
President & Principal Advisor
Bridging Consulting LLC

AGENDA

Bridging Consulting LLC

- Postmarket Risk Management Process
- Tools for Postmarket Risk Management
- Summary

Postmarket Risk Management Process

Risk Management

Throughout Total Product Lifecycle

Bridging Consulting LLC

Risk Management:

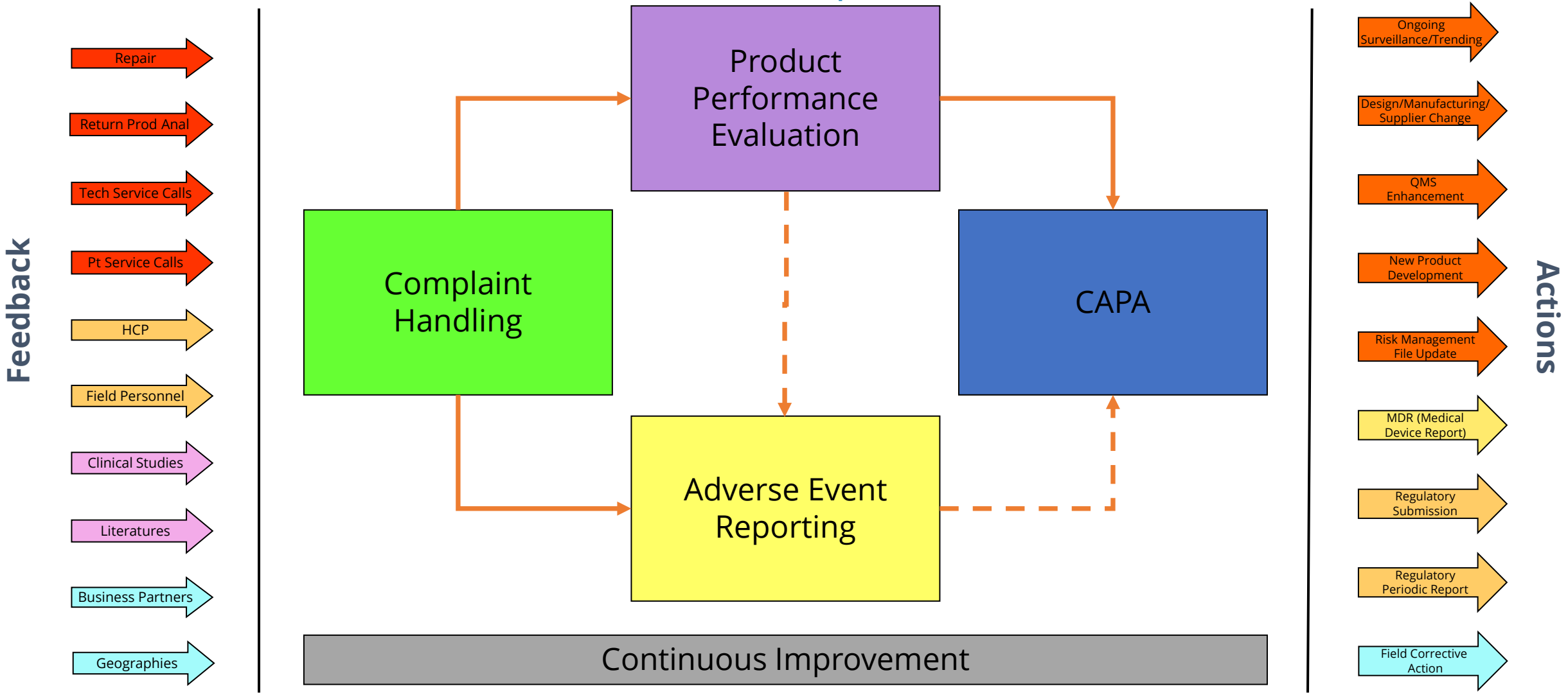
"systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk."

(ISO 14971:2019)

Risk Management Process

Postmarket Surveillance & Continuous Improvement

Bridging Consulting LLC



Postmarket Surveillance

Complaint Handling

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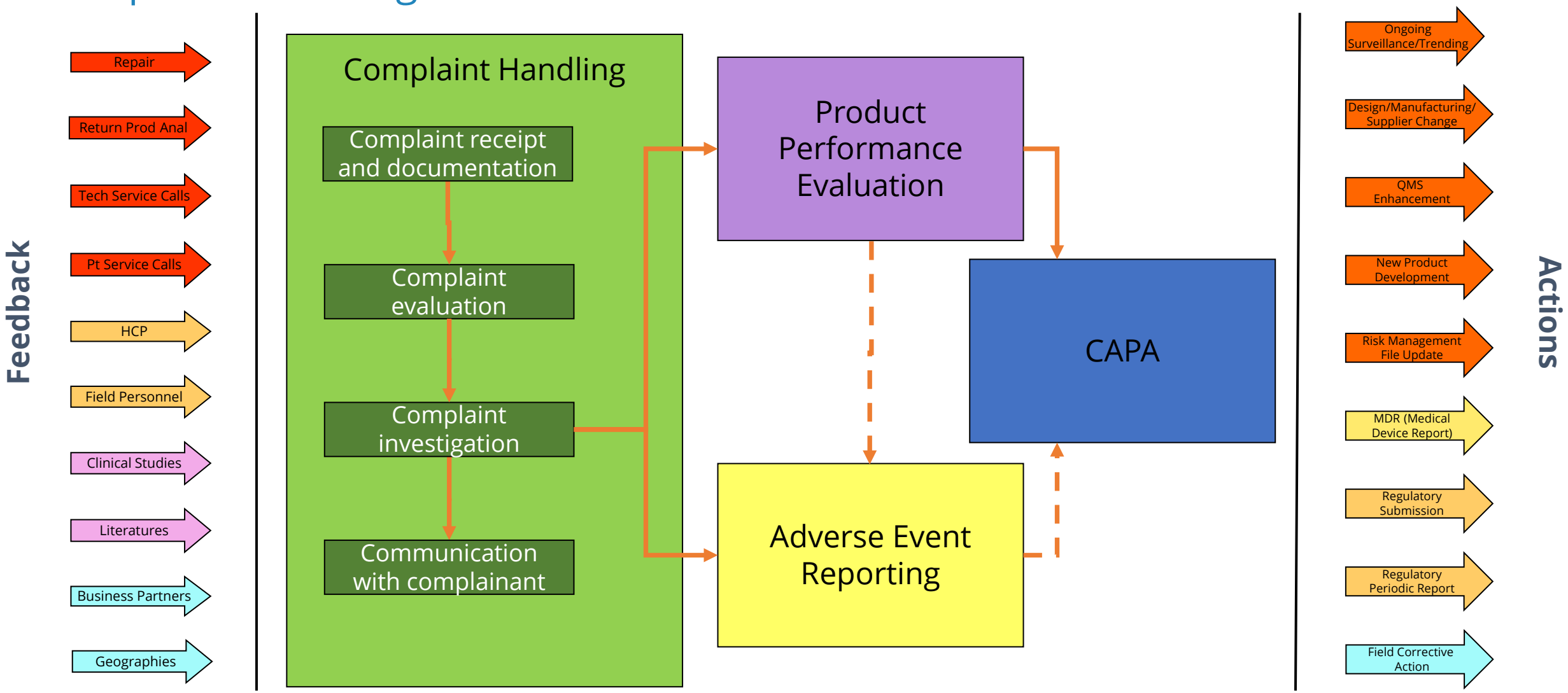

Postmarket Surveillance

Adverse Event Reporting

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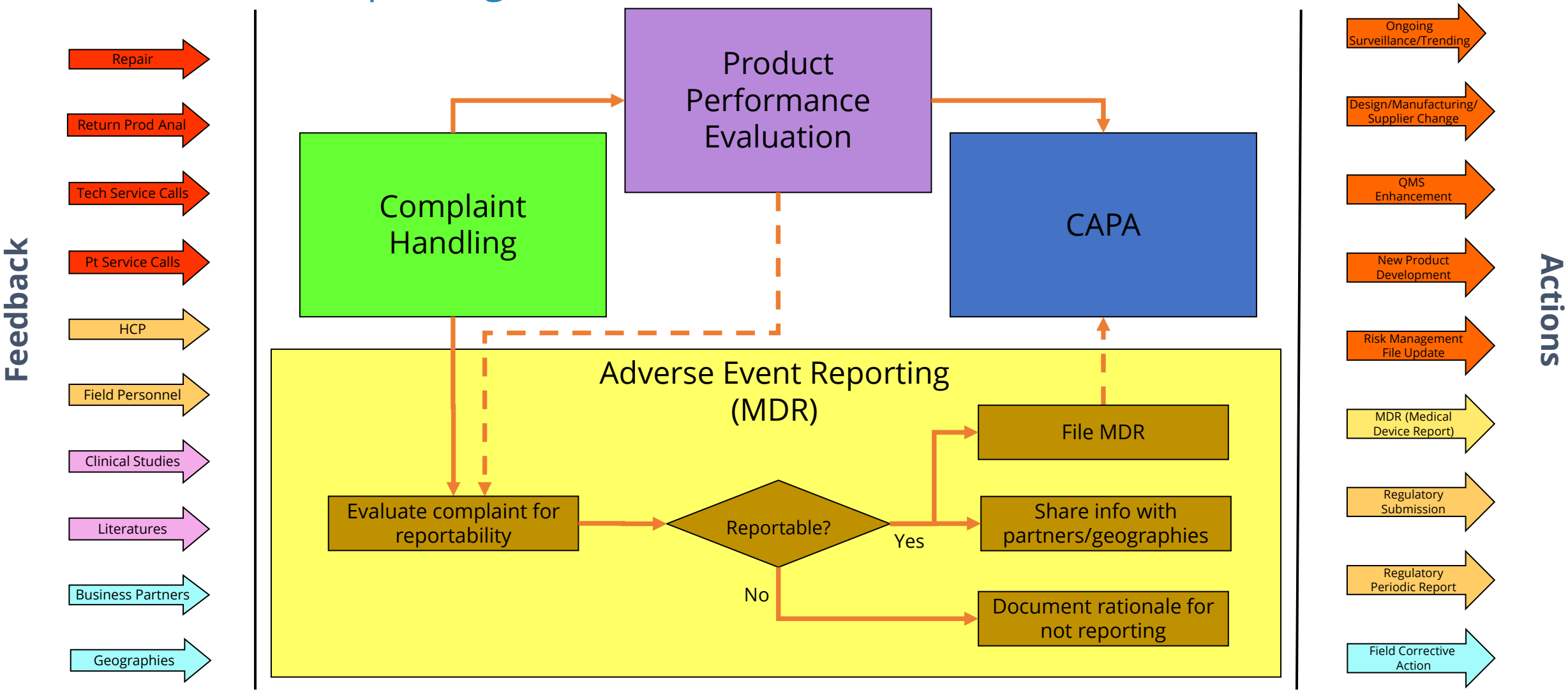

Postmarket Surveillance

Product Performance Evaluation

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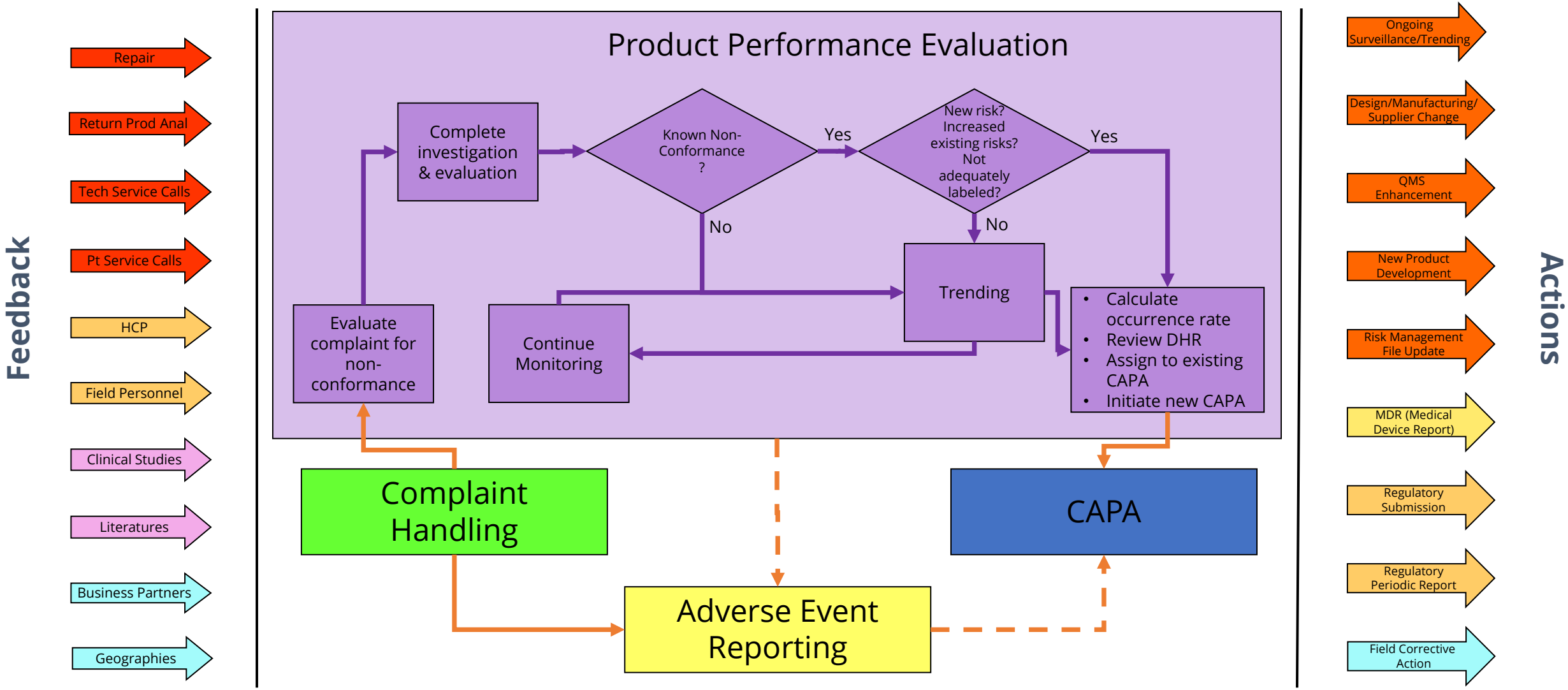

Postmarket Surveillance

Correct Actions & Preventive Actions (CAPAs)

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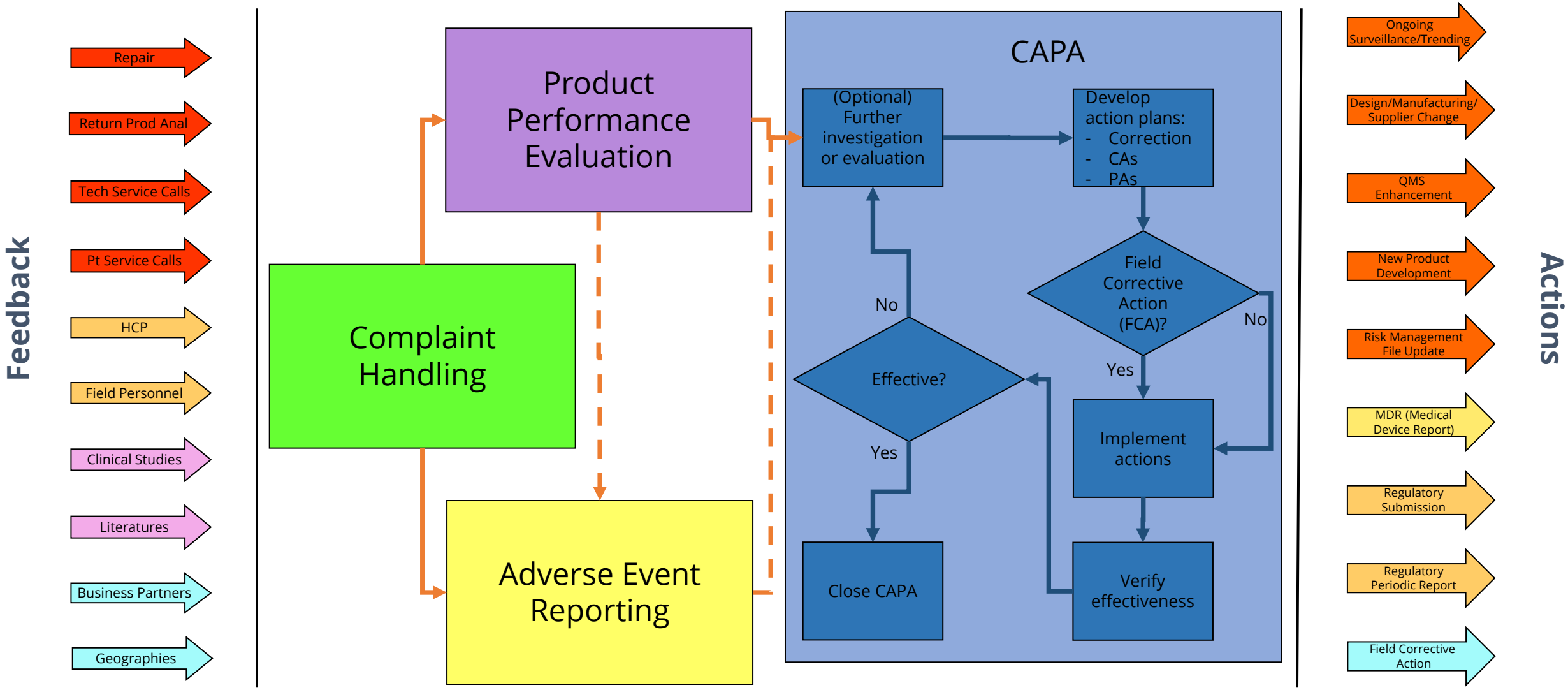

Continuous Improvement

Change Management

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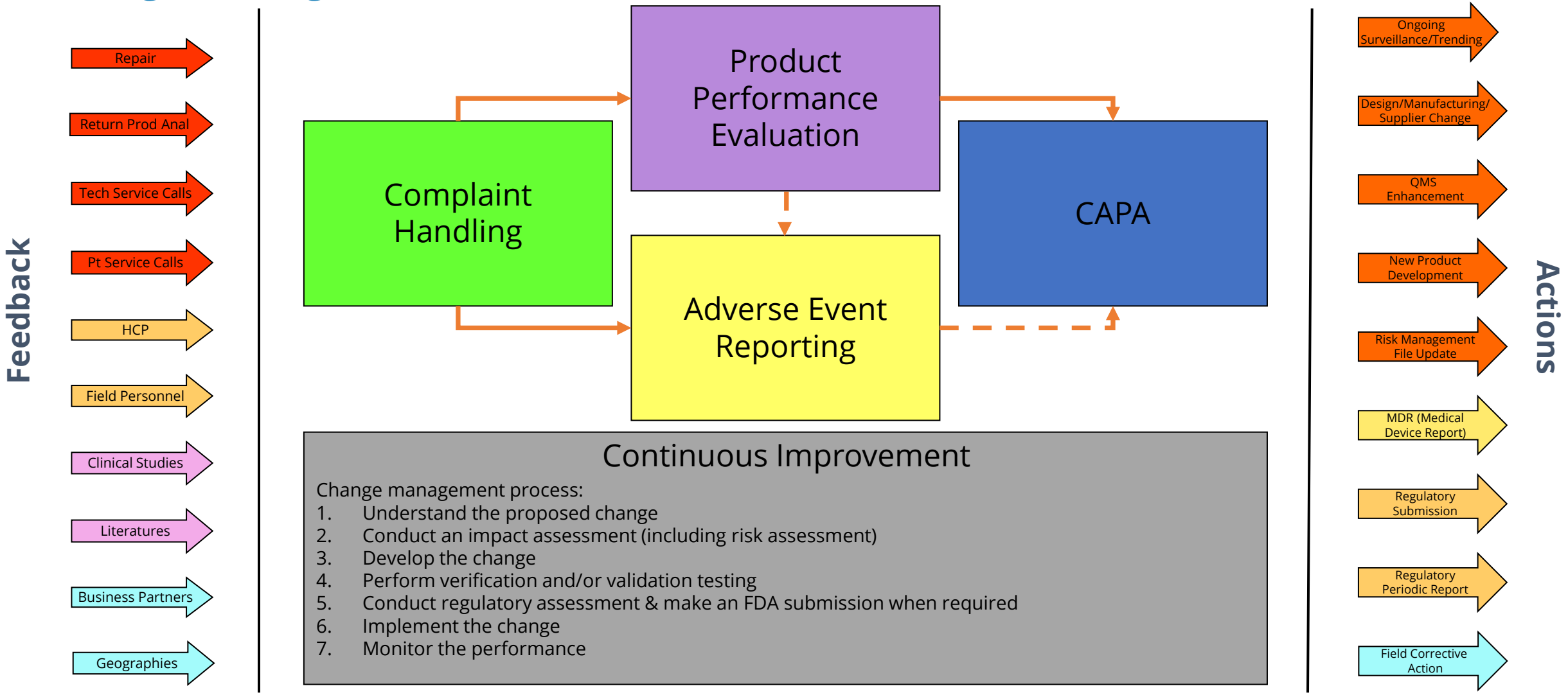


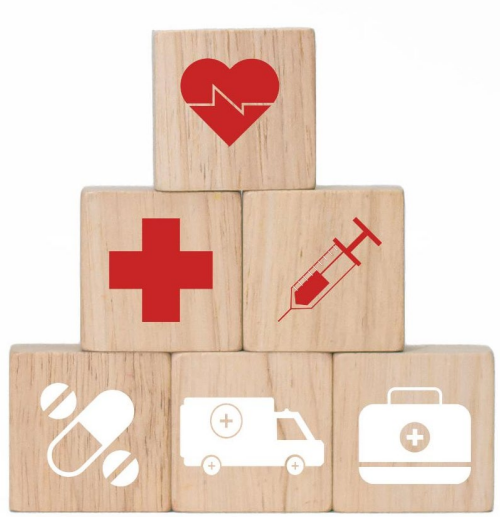
Tools for Postmarket Risk Management

Risk Management Tools

Unique for Postmarket

Bridging Consulting LLC

- Planning
  - Postmarket surveillance plan
  - Postmarket risk management plan
  - Postmarket cybersecurity management plan
- Data Collection
  - Patient registry
  - Literature search
  - Social media
  - Complaint handling system
  - Backend software analytics
- Reporting
  - Adverse event & product malfunction reporting system
  - Periodic safety update report (PSUR)
  - Postmarket clinical follow-up (PMCF)
  - PMA annual report
  - Post-approval study report
  - Recall report (FDA 806 report)



Risk Management Tools

Unique for Postmarket (cont.)

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- Trending
  - Trend analysis
  - Statistical tools, e.g., statistical process control (SPC)
  - CAPA
- Actions
  - Health hazard evaluation (HHE)
  - Field safety notification, product removal, etc.
  - Other risk communication tool, e.g., customer newsletters, product labeling updates
  - Risk management file maintenance & update, clinical evaluation report (CER) updates
  - Unique device identification (UDI) database

Summary

Summary

Postmarket Risk Management Processes and Tools

Bridging Consulting LLC

- Effective postmarket risk management involves a suite of processes and tools to monitor, analyze, and address risks throughout product lifecycle
- Key processes and tools include:
  - Planning: PMS plan, postmarket RMP, etc.
  - Data collection (including complaint handling): monitoring tools
  - Regulatory reporting: reportability evaluation and communication tools
  - CAPA: statistical trending tools, field communication tools
  - Continuous improvement: risk management and change management tools
- These processes/tools are critical for maintaining patient safety, regulatory compliance, and fostering continuous improvement

Contact Information:

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President and Principal Advisor

Bridging Consulting LLC

SCAN ME

How Audits and the MDSAP program support QMS

Aligning Medical Device Regulation to Optimize Risk Management

Sept. 15-16, 2024

USC-APEC Center

Los Angeles, CA

Medical Device Single Audit Program (MDSAP)

The MDSAP program uses ISO 13485:2016 as the primary standard, but also includes specific requirements for each participating country.

- Five countries: Australia, Brazil, Canada, Japan, and the United States.
- Launched by the International Medical Device Regulators Forum (IMDRF) in **2014** as a pilot program, satisfying the requirements of the pilot program in December 2016.

MDSAP, Competent Auditors and QMS

- The MDSAP to allow **competent auditors** from MDSAP recognized Auditing Organizations (AOs) to conduct a single audit of a medical device organization's **quality management system** that will satisfy the requirements of the medical device Regulatory Authorities (RAs) participating in the MDSAP program.
- The MDSAP provides a certification that allows a medical device manufacturer's **QMS** to be audited using a single audit.
- **FDA** accepts MDSAP audit reports as a substitute for routine Agency inspections.

Auditing Organization Availability to Conduct MDSAP Audits and the MDSAP Certification

- https://www.fda.gov/medical-devices/medical-device-single-audit-program-mdsap/auditing-organization-availability-conduct-mdsap-audits

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

MDSAP
MEDICAL DEVICE SINGLE AUDIT PROGRAM

TÜV SÜD America

CERTIFICATE

No. QS6 114190 0003 Rev. 00

Certificate Holder: **Ustar Biotechnologies (Hangzhou) Ltd.**
Bldg 1,2&4, 611 Dongguan Road
Binjiang District
310053 Hangzhou, Zhejiang Province
PEOPLE'S REPUBLIC OF CHINA

Certification Mark:

Scope of Certificate: **Design and Development, Manufacture, Distribution, Servicing of In-Vitro Diagnostic Nucleic Acid Test Kits and Reagents (including Home Use, Professional Use, Point of Care In-Vitro Diagnostic Medical Devices), Nucleic Acid Amplification and Detection Analyzers, Molecular Diagnostic Testing System (including Professional Use, Point of Care In-Vitro Diagnostic Medical Devices), Nucleic Acid Extraction Devices and Sample Collection Devices used in the Detection of Disease Status and Transmissible Agents**

Standard(s): **ISO 13485:2016**

Regulatory Authority(ies): **Australia TGA, Brazil ANVISA, Health Canada, USA FDA, MHLW / PMDA. See attached for listing of specific regulatory requirements.**

The Certification Body of TÜV SÜD America Inc. certifies that the quality management system of the manufacturer listed above has been audited against the stated criteria and found to conform to those criteria for the scope of certification listed. Validity of this certificate can be obtained by visiting the website www.tuvsud.com/ps-cert
TÜV SÜD America Inc. is an MDSAP Recognized Auditing Organization.

REPs Facility ID: **F005964**

Effective Date: **2022-10-27**

Expiry Date: **2025-10-26**

Date of Issue: 2022-11-02

(Renee Walker)
Manager, US Certification Body,
Medical and Health Services

TÜV®

TÜV SÜD America, Inc. • 401 Edgewater Place Suite #500 • Wakefield • MA 01880 • USA • www.tuvsud.com

Certificate GB21/968568

SYSTEM CERTIFICATION MDSAP SGS

The quality management system of

BPR Medical Ltd

22 Hamilton Way Mansfield Nottinghamshire NG18 5BU United Kingdom

Facility identification number : F003810

has been audited against the criteria stated below and found to conform to those criteria for the scope contained in this certificate

MDSAP (ISO 13485:2016)

Australia:
Therapeutic Goods (Medical Devices) Regulations, 2002, Schedule 3 Part 1 (excluding Part 1.6) – Full Quality Assurance Procedure [including design]
Brazil:
RDC ANVISA n. 16/2013 / RDC ANVISA n. 23/2012 / RDC ANVISA n. 67/2009
Canada:
Medical Devices Regulations – Part 1 SOR 98/282
Japan:
MHLW Ministerial Ordinance 169, Article 4 to Article 68 / PMD Act
United States:
21 CFR 820 / 21 CFR 803 / 21 CFR 806 / 21 CFR 807 – Subparts A to D

For the following activities and devices
Design, Manufacture and Service of medical gas therapy devices for respiratory therapy and for pain management.

This certificate is valid from
Effective Date: 19 April 2022 until Expiry Date: 07 February 2024
and remains valid subject to satisfactory surveillance audits.
Re certification audit due before 03 January 2024

Issue 3. Certified since 20 April 2021.

Authorised by

L. Henderson

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Regulatory Requirements

- United States
  - 21 CFR 820* Quality System Regulation
  - 21 CFR 803 Medical Device Reporting
  - 21 CFR 806 Reports of Corrections and Removals
  - 21 CFR 807 Establishment Registration And Device Listing For Subparts A to D Manufacturers And Initial Importers Of Devices
  - 21 CFR 821 (where applicable) Medical Device Tracking Requirements
- https://www.fda.gov/medical-devices/medical-device-single-audit-program-mdsap/mdsap-au-p0026-certificate-document-requirements

MDSAP	Policy Title: MDSAP AUDIT APPROACH	Document No: MDSAP AU P0002.009 Revision Date: 2024-08-06

MDSAP
MEDICAL DEVICE SINGLE AUDIT PROGRAM

AUDIT APPROACH

USC Mann
Alfred E. Mann School of Pharmacy
and Pharmaceutical Sciences

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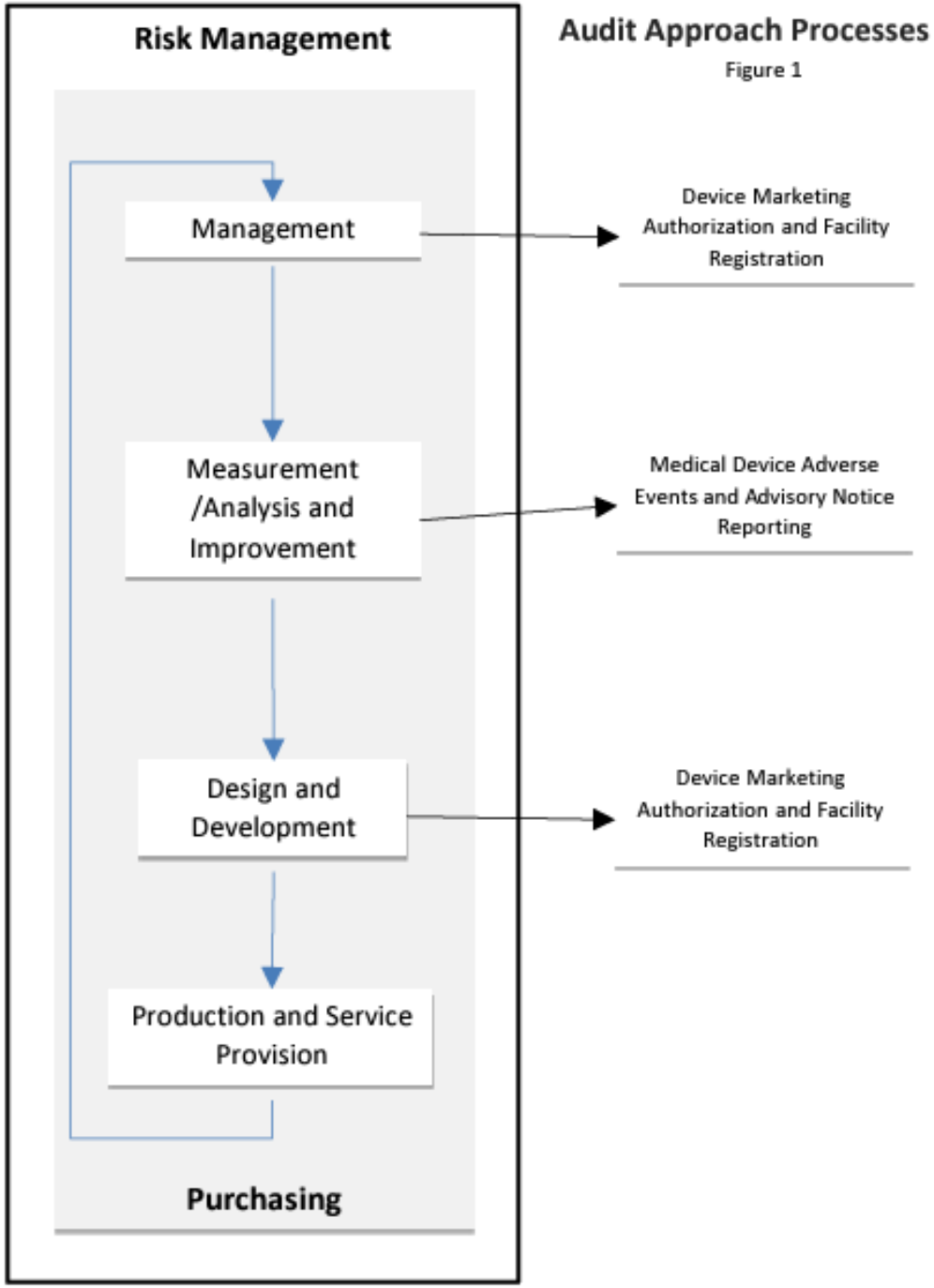
MDSAP Audit Sequence

- Management
- Measurement, Analysis and Improveme
- Design and Development
- Production and Service Controls



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Processes Audited

Chapter 1 - Management

ISO 13485:2016, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.1.5, 4.2.1, 4.2.2, 4.2.4, 4.2.5, 5.1, 5.2, 5.3, 5.4.1, 5.4.2, 5.5.1, 5.5.2, 5.5.3, 5.6, 6.1, 6.2, 7.1, 7.2.1, 7.2.3

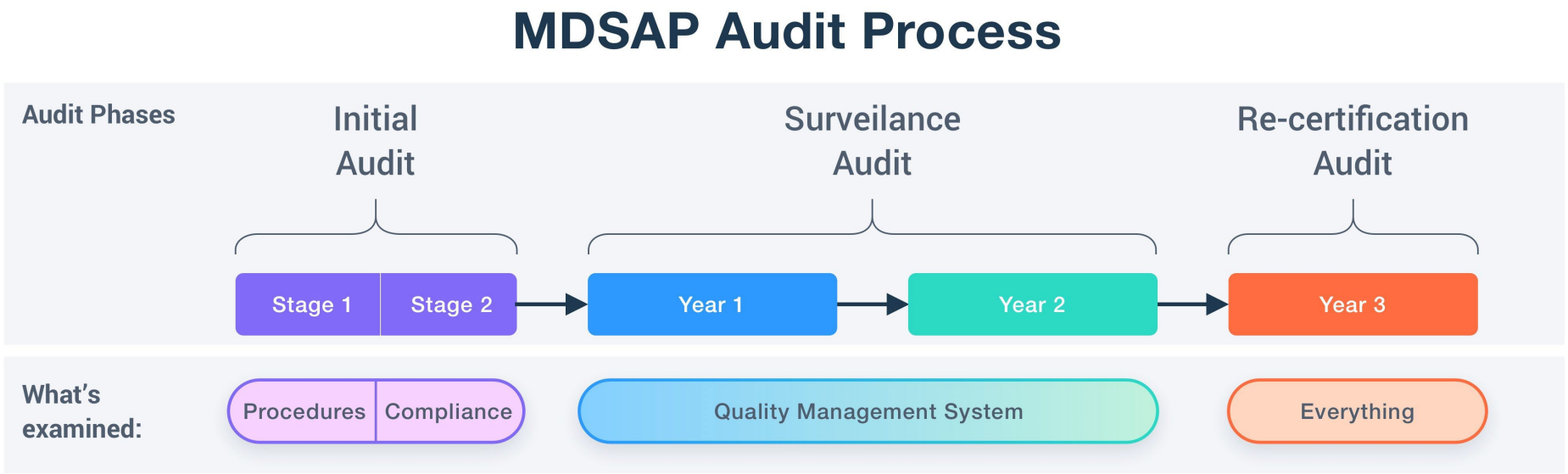
Description of the audited process or activity

Next visit plan

Date	Auditor	Time	Area/process	Clause
			Opening Meeting	
			Changes to QMS, Product, Organization, Follow-up from Previous Assessment	ISO 13485:2016, 4.1, 5.1, 5.2, 5.3, 5.4, 5.5, 8.5.1
			Chapter 1 - Management	
			Task 1 – QMS Planning, Implementation, Changes and Quality Manual	ISO 13485:2016, 4.1.1, 4.1.2, 4.1.3, 4.1.4, 4.2.2, 5.4.2
			Task 2 – Management Representative	ISO 13485:2016, 5.5.2
			Task 3 – Quality Policy and Quality Objectives	ISO 13485:2016, 5.3, 5.4.1
			Task 4 – Organizational Structure, Responsibility, Authority, Resources	ISO 13485:2016, 5.1, 5.5.1, 5.5.2, 6.1, 6.2
			Task 5 - Extent of Outsourcing	ISO 13485:2016, 4.1.5, 4.2.1
			Task 6 – Personnel Competency and Training	ISO 13485:2016, 4.2.1, 6.2
			Task 7 – Risk Management Planning and Review	ISO 13485:2016, 4.1.2, 7.1
			Task 8 – Document and Record Controls	ISO 13485:2016, 4.1.4, 4.2.1, 4.2.4, 4.2.5
			Task 9 – Management Reviews	ISO 13485:2016, 5.6
			Task 10 – Distribution of Devices with Appropriate Marketing	ISO 13485:2016, 4.1.1, 4.2.1, 5.2, 7.2.1, 7.2.3
			Task 11 – Top Management Commitment to Quality	ISO 13485:2016, 4.1.1, 4.1.4, 5.1, 5.5.3

MDSAP Three-Year Audit Cycle

- An initial audit,
- Surveillance audit in year one
- Surveillance audit in year two
- Re-audit in year three



https://blog.sterrastass.com/medical-device-single-audit-program-masap-explained

FDA Finalizes Rule Incorporating ISO 13485 into New Quality Management System Regulation (QMSR)

- On January 31, 2024
- The FDA issued a final rule amending the device current good manufacturing practice (CGMP) requirements of the Quality System (QS) Regulation under 21 CFR 820
  - To align more closely with the international consensus standard for Quality Management Systems for medical devices used by many other regulatory authorities around the world.
- This rule amends 21 CFR 820 by incorporating by reference the quality management system requirements of ISO 13485:2016
  - The international standard specific for medical device quality management systems set by the International Organization for Standardization (ISO)

Discussion Questions

- What is your experience with the MDSAP?
  - Are you involved as a regulator, manufacturer, or consultant?
- Do you agree that MDSAP indeed offers benefits? Such as reduced regulatory burden? Improved audit quality?
- Do you agree that MDSAP audit reports are sent to all participating members?

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In Vitro Diagnostic Devices: Special Risk Considerations

Christie Hughes, MPH, MLS(ASCP), RCC-IVDR

Principal Consultant, Qserve Group

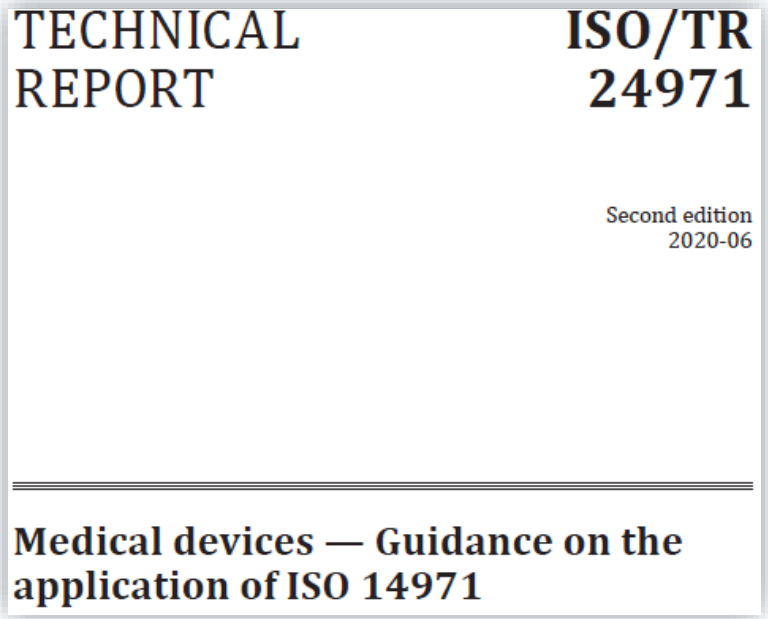
Structure

Section
Risk Management Process
In Vitro Diagnostics Overview
Known and Foreseeable Hazards and Hazardous Situations for IVDs
Identify Hazards & Hazardous Situations Related to Intended Use & Device Description for IVDs
Identify & Evaluate Potential Harms for IVDs
Summary

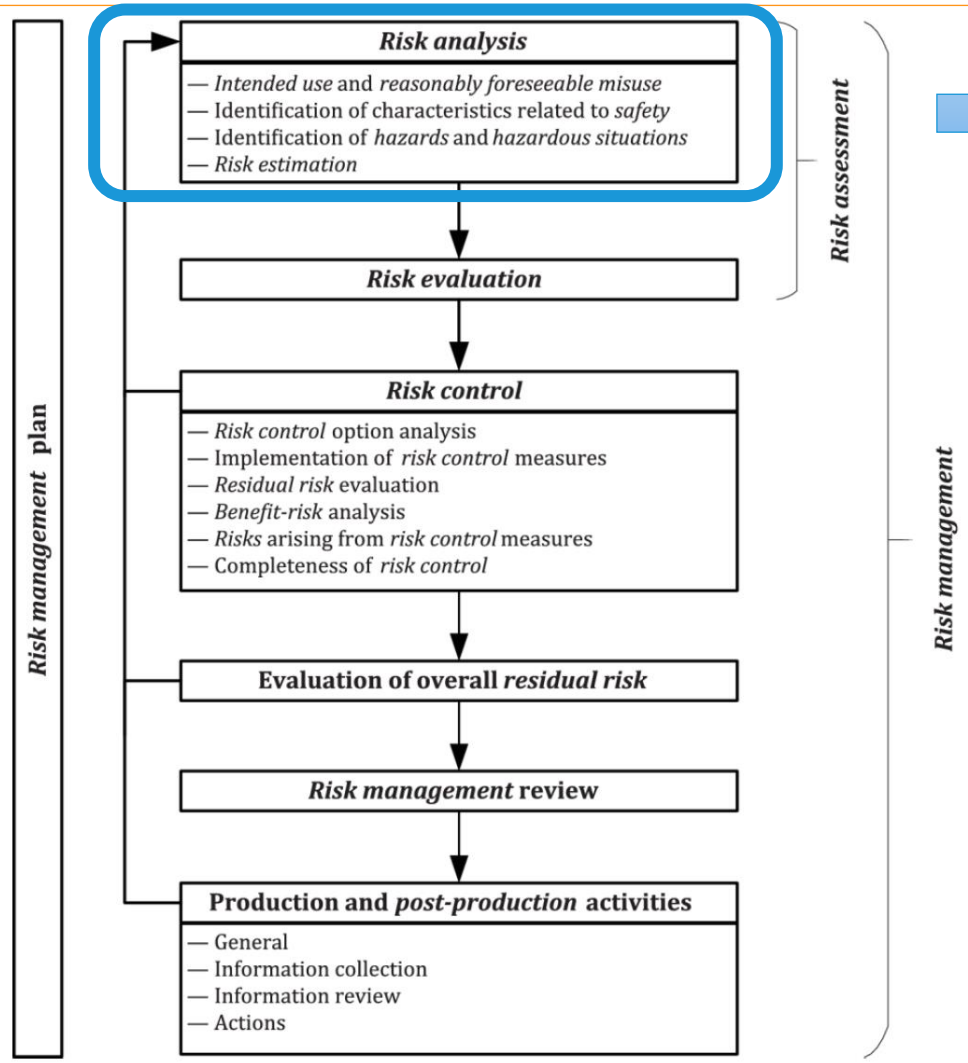
Risk Management Process

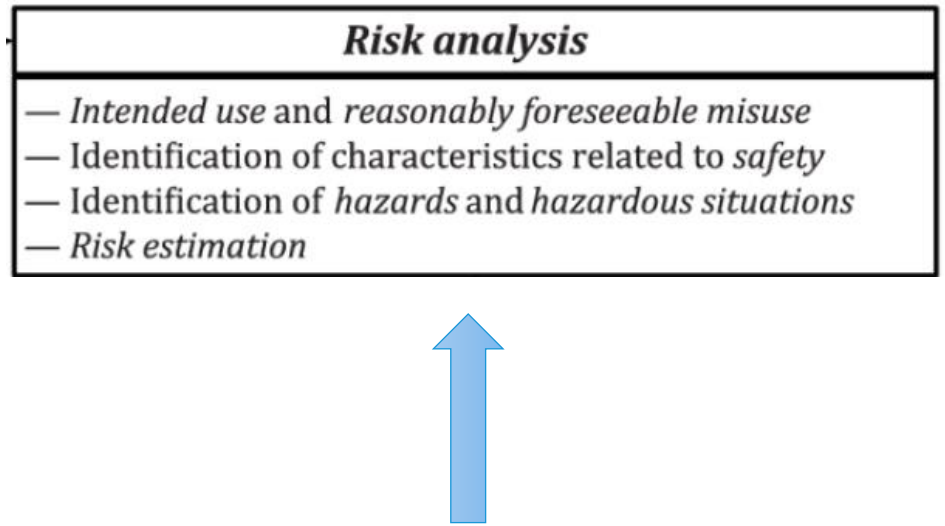
Overview of Risk Management for IVDs

- **Manufacturers should establish processes for risk management (RM) of IVDs in accordance with:**
  - ISO 14971:2019
  - Applicable regulations
    - Local regulations
    - Regulations of jurisdictions targeted for commercial distribution (e.g., EU IVDR)
- **Guidance for establishing, implementing, and maintaining a RM process is provided in ISO/TR 24971:2020**
  - Specific guidance for IVDs is provided in Annex H



Risk Management Process (ISO 14971)





The overall RM process remains the same for IVDs, but parts of the process are carried out differently for IVDs.

.....the practical approach

ISO 14971:2019, Figure 1 — A schematic representation of the risk management process

In Vitro Diagnostics Overview

In Vitro Diagnostic (IVD) Medical Device Definition

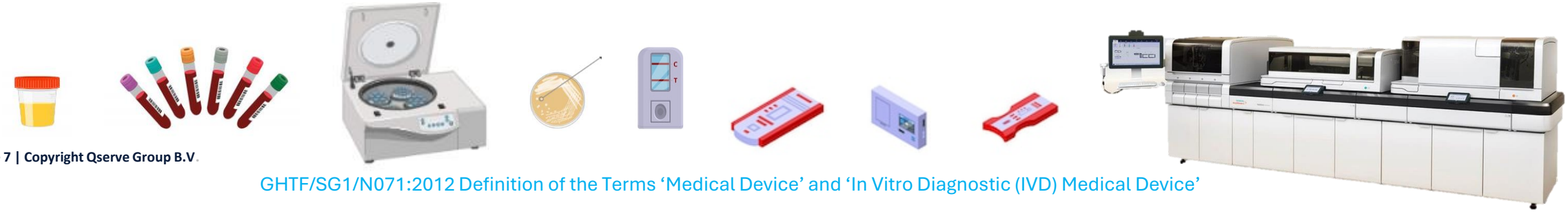
'In Vitro Diagnostic (IVD) medical device' means a medical device, whether used alone or in combination, intended by the manufacturer for the in-vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes.

- Note 1: IVD medical devices include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles and are used, for example, for the following test purposes: diagnosis, aid to diagnosis, screening, monitoring, predisposition, prognosis, prediction, determination of physiological status.
- Note 2: In some jurisdictions, certain IVD medical devices may be covered by other regulations.

Do not forget that standalone software can be an IVD medical device!

'Accessory to an IVD medical device' means an article intended specifically by its manufacturer to be used together with a particular IVD medical device to enable or assist that device to be used in accordance with its intended use.

- Note: Some jurisdictions include 'accessories to a medical device' and 'accessories to an IVD medical device' within their definitions of 'medical device' or 'IVD medical device', respectively. Other jurisdictions do not adopt this approach but still subject an accessory to the regulatory controls (e.g. classification, conformity assessment, quality management system requirements etc.) that apply to medical devices or IVD medical devices.



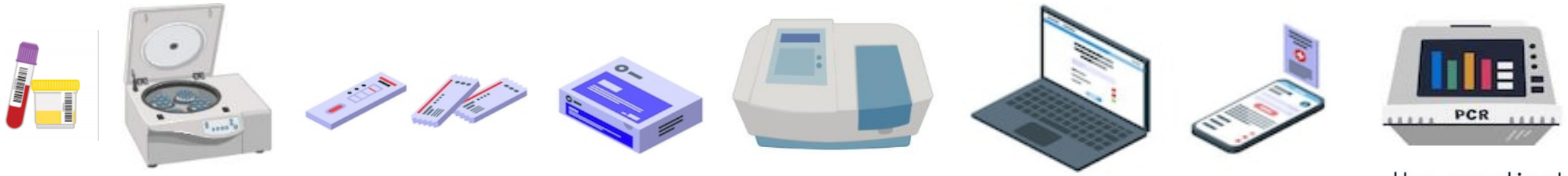
GHTF/SG1/N071:2012 Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device'

IVDs are *In Vitro*

- **Most IVDs do not come into contact with patients**
  - This session will consider all IVDs as *in vitro*
  - Where IVDs include invasive components, these should be assessed for risks similar to invasive non-IVD medical devices
- **IVDs present indirect risks to patients**
  - Incorrect test results
  - Delayed test results
- **IVDs can present direct risks to other stakeholders**
  - Biohazard risks (handling IVD reagents)
  - Electromechanical risks (interacting with IVD instruments)

***In vitro* exceptions may include:**

- **Specimen collection devices**
- **Point of care (POC) tests**
- **Near-patient tests (NPT)**
- **Self tests**
- **Home or over-the-counter (OTC) tests**



IVD Stakeholders

Manufacturing operators

- Produce & assemble devices

Service operators

- Install & maintain devices that are equipment or software

Laboratory operators

- Perform the tests

Clinicians

- Order tests, receive & interpret test results to inform patient management

Patients

- Receive or do not receive therapy from their clinician based on the test results

Each stakeholder and their interface with the IVD should be considered when assessing risk

Analytical User

Clinical User

ISO 14971, Annex H focuses on two users

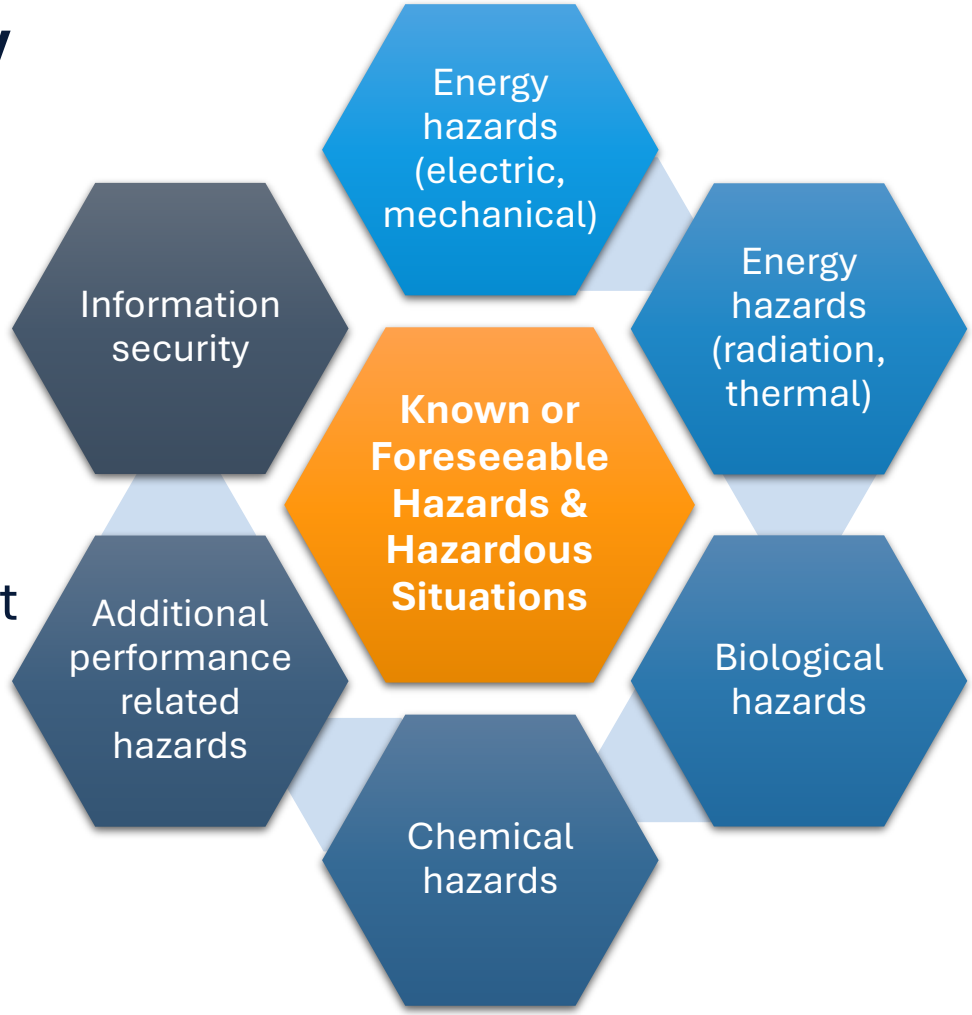
Analytical and/or Clinical User for Self or Home Tests

Any of these stakeholders could face hazardous situations that if not controlled, could lead to harm

Known and Foreseeable Hazards and Hazardous Situations for IVDs

Known and Foreseeable Hazards and Hazardous Situations for General Medical Devices

- **Clinicians and patients do not typically interact physically with IVDs**
  - Exceptions to this include POC, NPT, self and home tests
- **ISO 14971:2019, Annex C, Table C.1 provides examples of known and foreseeable hazards that typically apply to non-IVD devices**
  - These may still apply to IVDs, but direct impact is toward manufacturing, service, and/or lab operators.
  - These hazards can indirectly impact patients as part of the sequence of events (hazardous situation) leading to an IVD hazard.



Known and Foreseeable Hazards to Patients

Incorrect examination result

- False positive or negative
- False increased or decreased value

Delayed examination result

- May impact time-critical patient management

Incorrect information accompanying result

- May impact results interpretation & use by clinician

Inappropriate medical intervention that can result in harm

Lack of medical intervention necessary to prevent harm

ISO/TR 24971:2020, Annex H, section H2.3

Known and Foreseeable Hazardous Situations for IVDs

- **Annex H of ISO/TR 24971:2020 lists example hazardous situations that could lead to typical IVD patient hazards.**
- **Manufacturers should review these to determine whether these may apply to their device.**
- **For those that apply, manufacturers should:**
  - Identify the sequence of events that could lead to the situation
  - Identify which IVD patient hazard could occur, e.g., incorrect result, delayed result, or incorrect information accompanying the result.

- Hazardous situations from fault conditions
- Digital technology failures
- Failures leading to a delay of results when the IVD is used with digital software applications
- Hazardous situations from normal use
- Hazardous situations from use errors, including use errors for POC and self/home tests
- Hazardous situations from reasonably foreseeable misuse, including misuse by patients performing self/home tests

ISO/TR 24971:2020, Annex H, section H2.3

Identify Hazards & Hazardous Situations Related to Intended Use & Device Description for IVDs

Identify Hazards/ Hazardous Situations Related to Intended Use & Device Description

- **Identify and review the device's intended use and planned configuration to determine possible hazards and hazardous situations from use of the device as intended.**
- **Consider:**
  - Intended use statement
  - Test workflow
  - Device configuration
  - Specimen type(s)
  - Analytical use
  - Clinical use

Identify IVD Intended Use

Intended use for legacy IVDs may be vague

- **Intended Use/ Purpose** - The objective intent of the manufacturer regarding the use of a product, process or service as reflected in the specifications, instructions and information provided by the manufacturer.
  - Should be sufficiently detailed to allow appropriate evaluation of the device's risk classification and to help assess the possible risks associated with the device.

What is…	Specify…
…being detected or measured?	…whether or not the test is automated
…the intended function (e.g., screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, or companion diagnostic)	…whether test is qualitative, semi-quantitative, or quantitative
	…who is the intended user?
	…the intended patient population
…the specific disorder, condition, or risk factor the test is intended to detect, define, or differentiate	…the intended specimen type
	…whether the device is intended for single or multiple use
	…for companion diagnostics the associated medicinal product

These details will help the manufacturer to identify potential hazards and hazardous situations related to their device.

GHTF/SG1/N77:2012, GHTF/SG5/N6:2012, IMDRF/RPS WG/N13 FINAL:2024

Typical IVD Workflow

Clinician orders test

Specimen may be transported & stored

Collect specimen from patient

Prepare specimen for testing

Perform test

Review results

Report results to clinician

Patient management

.....the practical approach

Workflow Considerations for IVDs

- Intended use/ indications for use
- Limitations (contraindications for use)

Clinician orders test

Collect specimen from patient

- Collection procedure
- Collection device(s)
- Specimen stability

- Transport packaging
- Transport conditions
- Storage conditions

Specimen may be transported & stored

Prepare specimen for testing

- Pre-analytical steps
- Prepared sample stability
- Reagents & equipment

- Qualitative/ quantitative
- Automated or manual
- Potential interferents
- Device interfaces
- Operator profile

Perform test

Review results

- Test interpretation
- Medical decision points
- Clinical significance of delayed results

- Clinician result interpretation
- Use in patient management
- Possible actions taken on abnormal/ unexpected results

Report results to clinician

Patient management

.....the practical approach

Device Configuration Considerations for IVDs

- **Is the device used alone or in combination with other devices?**
- **Does device consist of or contain software?**
  - Does software provide diagnostic or treatment recommendations?
  - Does software employ artificial intelligence/machine learning?
- **Does device require other reagents or equipment not provided by the manufacturer?**
- **How are results communicated to clinicians (especially for self/home tests)?**
- **Is device a companion diagnostic (CDx)?**
- **How is device distributed or put into service?**
  - How is device packaged to retain its integrity?
  - How is device shipped? What are the transport conditions?

Device Configuration Hazardous Situation Example

What are some possible hazardous situations related to device configuration?

Device	BIOFIRE® Blood Culture Identification 2 (BCID2) Panel
Intended use	The BIOFIRE® Blood Culture Identification 2 (BCID2) Panel is a multiplexed nucleic acid test intended for…the simultaneous qualitative detection and identification of multiple bacterial and yeast nucleic acids and select genetic determinants associated with antimicrobial resistance. The BIOFIRE BCID2 Panel test is performed directly on blood culture samples identified as positive by a continuous monitoring blood culture system. Results are intended to be interpreted in conjunction with Gram stain results.
Recall reason	**Increased risk of false positive Serratia marcescens results when the BIOFIRE BCID2 Panel is used with certain lots of BACT/ALERT Culture Bottles**
Hazardous situation	• Test detects nucleic acid from viable and non-viable organisms alike • BACT/ALERT Culture Bottles have an increased level of non-viable organism from Serratia marcescens targets • Patient blood culture identified as positive for a microbe by a continuous monitoring blood culture system • BCID2 test detects Serratia marcescens (and possible other microbes) from positive blood culture sample • Lab fails to identify false positive result for Serratia marcescens • Lab reports false positive result for Serratia marcescens • Clinician receives false positive result for Serratia marcescens • Patient is symptomatic for infection • Clinician accepts incorrect result(s) • Clinician administers antibiotic based on false positive result for Serratia marcescens which may not be effective for other identified microbes from positive blood culture
Hazard(s)	**Incorrect examination result** (false positive result for bacteria from culture media)
Potential harm	Patient infection worsens due to inappropriate or ineffective antibiotic therapy Patient exposed to unnecessary antibiotic therapy

IVD relies on combination use with blood culture bottle manufactured by another vendor. Compatibility should be ensured and continually evaluated.

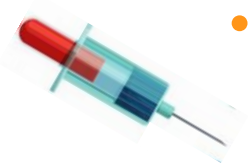
US Recall Number Z-2456-2024; Recall Event ID 94886

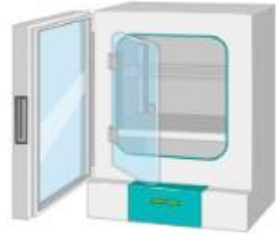
UK MHRA Field Safety Notice FSCA - FIELD SAFETY CORRECTIVE ACTION FA-TWD-000005

Specimen Type Considerations for IVDs

- **What is the collection procedure and associated collection device(s)?**
  - Does device allow multiple options for collection devices/receptacles?

- **Does device allow testing with multiple specimen types?**
- **How much time is allowed between specimen collection and performing the test?**
  - How will the specimen be stored (duration, conditions) to ensure integrity?
- **Will the specimen be transported from one location to another before testing?**
  - What are the anticipated transport duration, method, and conditions?





Specimen Type Hazardous Situation Example

What are some possible hazardous situations related to specimen type?

Device	VITROS Immunodiagnostic Products Folate Reagent Pack 1/2
Intended use	For the quantitative measurement of folate in human serum and plasma (heparin) and whole blood (red cell folate) using the VITROS ECi/ECiQ/3600 Immunodiagnostic Systems and the VITROS 5600/XT 7600 Integrated Systems, to aid in the differential diagnosis of anemia.
Recall reason	**Fibrinogen in patient plasma samples precipitates out of solution upon the addition of folate stabilizer reagent as part of the pre-treatment process causing the increase in "TM5-4MA" or "TM5-4MB" condition codes which lead to a delay of results.**
Hazardous situation	• Folate stabilizer reagent within test kit precipitates fibrinogen in plasma samples • Plasma specimen (instead of serum or whole blood specimen) is ordered for testing folate • Patient plasma sample contains fibrinogen • Plasma specimen is used for testing folate • Fibrinogen in patient plasma specimen precipitates during pre-treatment portion of test procedure • Analyzer gives specific error codes and does not complete testing • Lab unable to obtain test result • Lab notifies clinician of no available result • Patient is symptomatic for anemia • Clinician is unable to evaluate folate as a contributor to anemia
Hazard(s)	**Delayed examination result** (unable to obtain result)
Potential harm	Patient anemia worsens due to inability to determine folate contribution to anemia Patient exposed to inappropriate anemia therapy

IVD claims ability to be used with plasma specimens, but it is not compatible with plasma specimens.

US Recall Number Z-2580-2024; Recall Event ID 95020
TGA Recall Reference RC-2024-RN-00604-1

Analytical Use Considerations for IVDs

- **What is the intended use?**
  - Analyte/biomarker detected/measured
  - Qualitative, semi-quantitative or quantitative result
  - Automated or manual test procedure
- **Are there pre-analytical steps required?**
  - Pre-analytical steps
  - Pre-analytical use environment
  - Prepared sample stability
  - Reagents & equipment

- **Can other substances possibly found in the intended specimen type(s) interfere with the test procedure?**
- **Does the device interface or connect with other devices?**
- **Who is the intended user (test operator)?**
  - Is the intended test operator a trained lab professional, non-lab healthcare professional, or lay person?
  - What qualifications or training is needed?
- **What is the use environment?**
  - E.g., medical laboratories, emergency room, operating room, ambulance, intensive care unit, neonatal care unit, nursing home, physician's office, screening clinics, or the patient's home?

Analytical Use Hazardous Situation Example

Device	**Atellica® CH Iron3 (Iron3) impacting:** **Atellica CH Cholesterol_2 (Chol_2), Atellica CH LDL Cholesterol (LDLC), and Atellica CH Triglycerides_2 (Trig_2)**
Intended use	The **Atellica® CH Iron3 (Iron3)** assay is for in vitro diagnostic use in the quantitative measurement of iron in human serum and plasma (lithium heparin and sodium heparin) using the Atellica® CH Analyzer. Iron measurements are used in the diagnosis and treatment of diseases such as iron deficiency anemia and other disorders of iron metabolism. • The **Atellica™ CH Cholesterol_2 (Chol_2)** assay - quantitative determination of cholesterol in human serum and plasma for use in the diagnosis and treatment of disorders involving excess cholesterol in the blood and in lipid and lipoprotein metabolism disorders. • The **Atellica® CH LDL Cholesterol (LDLC)** assay - quantitative determination of LDL cholesterol in human serum and plasma for use in the diagnosis and treatment of atherosclerosis. • The **Atellica® CH Triglycerides 2 (Trig_2)** assay - quantitative determination of triglycerides in human serum and plasma for use in the diagnosis and treatment of patients with diabetes mellitus, nephrosis, liver obstruction, other diseases involving lipid metabolism, or various endocrine disorders.
Recall reason	**The manufacturer confirmed the potential for falsely elevated Chol_2, LDLC, and Trig_2 results on the Atellica® CH and Atellica® CI analyzers when the previous result in the cuvette was Iron3. Internal studies demonstrated a positive bias ranging from 2-16%. This issue can impact calibrator, quality control (QC), and patient results. All future lots are impacted until further notice.**
Hazardous situation	• Atellica CH and Atellica CI analyzers use re-usable test cuvettes as reaction wells for assays performed on tne analyzers. • Design & use of Atellica CH Iron3 assay on Atellica CH and Atellica CI analyzers appears to leave residual agents that carry-over and interfere with other Atellica assays that are not fully removed from test cuvettes with available washing or maintenance routines. • Patient test for Iron3 is performed on Atellica CH or Atellica CI analyzer. • Patient test for Chol_2, LDLC, or Trig_2 is performed on Atellica CH or Atellica CI analyzer. • Analyzer generates falsely increased Chol_2, LDLC, or Trig_2 result. • Lab fails to detect incorrect result. • Lab reports falsely increased Chol_2, LDLC, or Trig_2 result. • Clinician receives incorrect Chol_2, LDLC, or Trig_2 result. • Patient is asymptomatic for conditions related to Chol_2, LDLC, or Trig_2 intended uses. • Clinician accepts incorrect result(s) as correct. • Clinician administers therapy based on incorrect Chol_2, LDLC, or Trig_2 result.
Hazard(s)	**Incorrect examination result** (false increased quantitative test result value)
Potential harm	Patient exposed to inappropriate therapy

IVD introduces substances that carry-over & interfere with performance of other assays from same manufacturer used on their analyzers that use re-usable test cuvettes.

US Recall Number Z-1549-2024; Recall Event ID 94260; MHRA reference: 31565659

Clinical Use Considerations for IVDs

- **What is the intended use?**
  - What is the test's function (e.g., screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic)?
  - What injury, illness or condition will the results be used to detect, diagnose, predict or monitor?
- **How will test results be used in patient management?**
  - Can clinicians recognize incorrect results
  - What actions would the clinician take in the event of an abnormal or unexpected result?
  - What is the clinical significance of delayed results?
  - What are the potential adverse consequences of unnecessary medical intervention?
- **Who will use the results (the "clinical user")?**
  - E.g., medical specialists, general clinicians, or patients?
  - What qualifications or training is needed?
  - Will specific training be required for the clinical user to interpret test results?
- **What are the medical decision points?**
  - What degree of accuracy is required at the medical decision points?
- **Can test performance or results be impacted by a security breach?**

.....the practical approach

Clinical Use Hazardous Situation Examples

- **What are some possible hazardous situations related to clinical use?**
- **Intended use**
  - The manufacturer did not demonstrate scientific validity for the test analyte related to any specific clinical condition, and did not perform clinical performance studies to demonstrate clinical utility.
  - The intended use statement does not relate the detected analyte to a specific clinical condition. It simply states the test is intended to detect/measure this analyte.
  - Clinician orders test and uses test results for patient management in a manner they see fit.
  - The patient experiences an adverse event based on this use of the test result to initiate unnecessary therapy.
  - While this use of the test was not intended by the manufacturer, it is also not contra-indicated in the labeling.
- **Medical decision points (MDP)**
  - The manufacturer did not sufficiently research clinical guidelines for the clinical conditions for which their test may be used in medical care.
  - The manufacturer claims an intended use for diagnosing or aiding in patient management of multiple conditions with this test.
  - The analytical and clinical performance studies performed by the manufacturer did not address accuracy and precision for all appropriate MDPs for the conditions claimed in the test's intended use.
  - Clinician orders test for a condition for which the MDPs were not sufficiently validated.
  - Clinician accepts the test result as accurate and determine that therapy is not necessary.
  - Patient's symptoms worsen leading to serious injury.

General Characteristics Related to Patient Safety

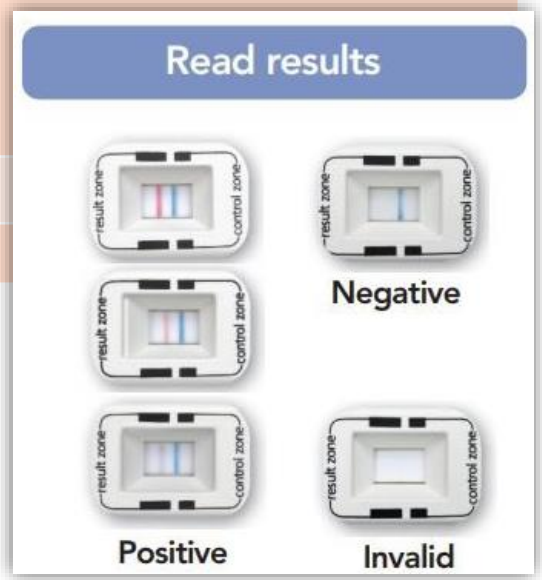
- **Will the device come into contact with the patient or other persons?**
- **Are the materials used within and to make the device compatible…**
  - With each other?
  - With materials the device is expected to come into contact with (e.g., specimens, other reagents, cleaning agents?
- **Does the IVD consist of or include equipment?**
  - Consider: electromechanical safety, electromagnetic compatibility, radiation exposure, battery safety, radio frequency/telecom safety, installation requirements, user & other equipment interfaces, etc.
- **Is calibration or maintenance required?**
  - Consider: calibration metrological traceability, calibration & maintenance schedules
- **Does IVD consist of or include software?**
  - Consider: integrity of installed software, data access & security, user interface usability, computing & mobile platforms, etc.
- **What is the device lifetime?**
  - Consider: reagent shelf life, equipment & component reliability
- **How will the IVD be manufactured?**
  - Consider: new required processes or equipment/technology, production scale, contract manufacturers & suppliers, etc.
- **What are the user requirements and needs for each user?**

General Characteristics Hazardous Situation Example (Manufacturing)

What are some possible hazardous situations related to general characteristics?

Device	InflammaDry MMP-9 Test
Intended use	InflammaDry is a rapid, immunoassay test for the visual, qualitative in vitro detection of elevated levels of the MMP-9 protein in human tears from patients suspected of having dry eye to aid in the diagnosis of dry eye in conjunction with other methods of clinical evaluation. This test is intended for prescription use at point-of-care sites.
Recall reason	**There are two windows on the test device, the control line window and the test results window. The line for the test results window were misaligned. In instances of positive test results, the positive test line may not be visible/ hidden under the cassette of the test device thus potentially leading to a false negative result.**
Hazardous situation	• Test membrane not correctly aligned in test cassette window • Healthcare provider (HCP) administering test fails to identify misaligned membrane in cassette • HCP administers test on patient • Cassette reports positive control line and positive result line with positive result line not visible in the test result window • HCP interprets false negative result • Patient has dry eye symptoms • HCP/clinician relies on test results for patient management • HCP/clinician does not administer therapy for dry eye
Hazard(s)	**Incorrect examination result** (false negative result)
Potential harm	Patient symptoms of dry eye worsen; continued dry eye disease/symptoms leads to corneal abrasions

IVD's manufacturing & QC processes do not ensure consistent manufacture of a safe & effective device.



US Recall Number Z-1637-2024; Recall Event ID 94219

Performance Characteristics Related to Patient Safety

Trueness of the measured values	• Bias, traceability to a reference standard
Measurement precision	• Repeatability, intermediate precision, reproducibility
Analytical specificity	• Quantitative/semi-quantitative - influence of interfering or cross-reacting substances • Qualitative - fraction of true negative results in samples containing the analyte
Analytical sensitivity	• Quantitative/semi-quantitative - ability to discriminate between quantity limits or ranges • Qualitative - fraction of true positive results in samples containing the analyte
Detection limit	• Lowest quantity that can be reliably detected
Quantitation limit	• Lowest quantity that can be accurately measured
Measuring interval	• Range of values over which the analytical performance was validated
Diagnostic sensitivity	• Fraction of true positive results in patients with disease
Diagnostic specificity	• Fraction of true negative results in patients without disease

Performance Characteristics Hazardous Situation Example

Device	ADVIA Chemistry Microalbumin_2 (µALB_2)
Intended use	For in vitro diagnostic use in the quantitative measurement of microalbumin in human urine on ADVIA® Chemistry systems. Such measurements are used in the diagnosis and treatment of microalbuminuria and are helpful for the detection and treatment of patients at risk from renal disease.
Recall reason	**Certain lots of the ADVIA® Chemistry Microalbumin_2 (µALB_2) assay are not meeting the Prozone Effect (hook effect) claim in the IFU on the ADVIA® 1800 Chemistry Systems, ADVIA® 2400 Chemistry Systems, and ADVIA® Chemistry XPT Systems.** • The assay's **Analytical Measuring Range is from 0.3 mg/dL (3 mg/L) to** the level 5 ADVIA Chemistry Microalbumin_2 Calibrator, which varies **from 38.0–42.0 mg/dL (380–420 mg/L)**. • **The IFU states that "A prozone effect was not demonstrated for analyte concentrations up to 20,000 mg/dL (200,000 mg/L)."** **However, for certain lots, erroneously depressed microalbumin patient results may occur:** • For ADVIA 1800 Chemistry Systems: the **prozone effect claim began to fail at concentrations greater than 274 mg/dL (2,740 mg/L).** As a **worst-case scenario, a sample at 4,060 mg/dL (40,600 mg/L) could be reported as low as 20.6 mg/dL (206 mg/L).** • For ADVIA 2400 Chemistry Systems: the **prozone claim began to fail at concentrations greater than 6,480 mg/dL (64,800 mg/L).** As a **worst-case scenario, a sample at 19,440 mg/dL (194,400 mg/L) could be reported as low as 10.8 mg/dL (108 mg/L).**
Hazardous situation	• Certain lots of the IVD do not meet performance claims in labeling. • Patient specimen contains elevated microalbumin (e.g., 300 mg/dL). • ADVIA µALB_2 assay is performed on specimen using the ADVIA 1800 Chemistry System. • Analyzer generates falsely decreased result (appears in normal range). • Lab fails to detect incorrect result. • Lab reports falsely decreased microalbumin result. • Clinician receives incorrect microalbumin result. • Patient has mild symptoms for renal disease. • Clinician accepts incorrect result as correct, which appears to be in the normal range. • Clinician elects not to administer therapy based on incorrect result.
Hazard(s)	**Incorrect examination result** (falsely decreased result)
Potential harm	Patient's symptoms worsen progressing to renal disease

IVD component specifications or QC may be insufficient to detect when performance claims are not met.

MHRA reference: 31584267

Identify & Evaluate Potential Harms for IVDs

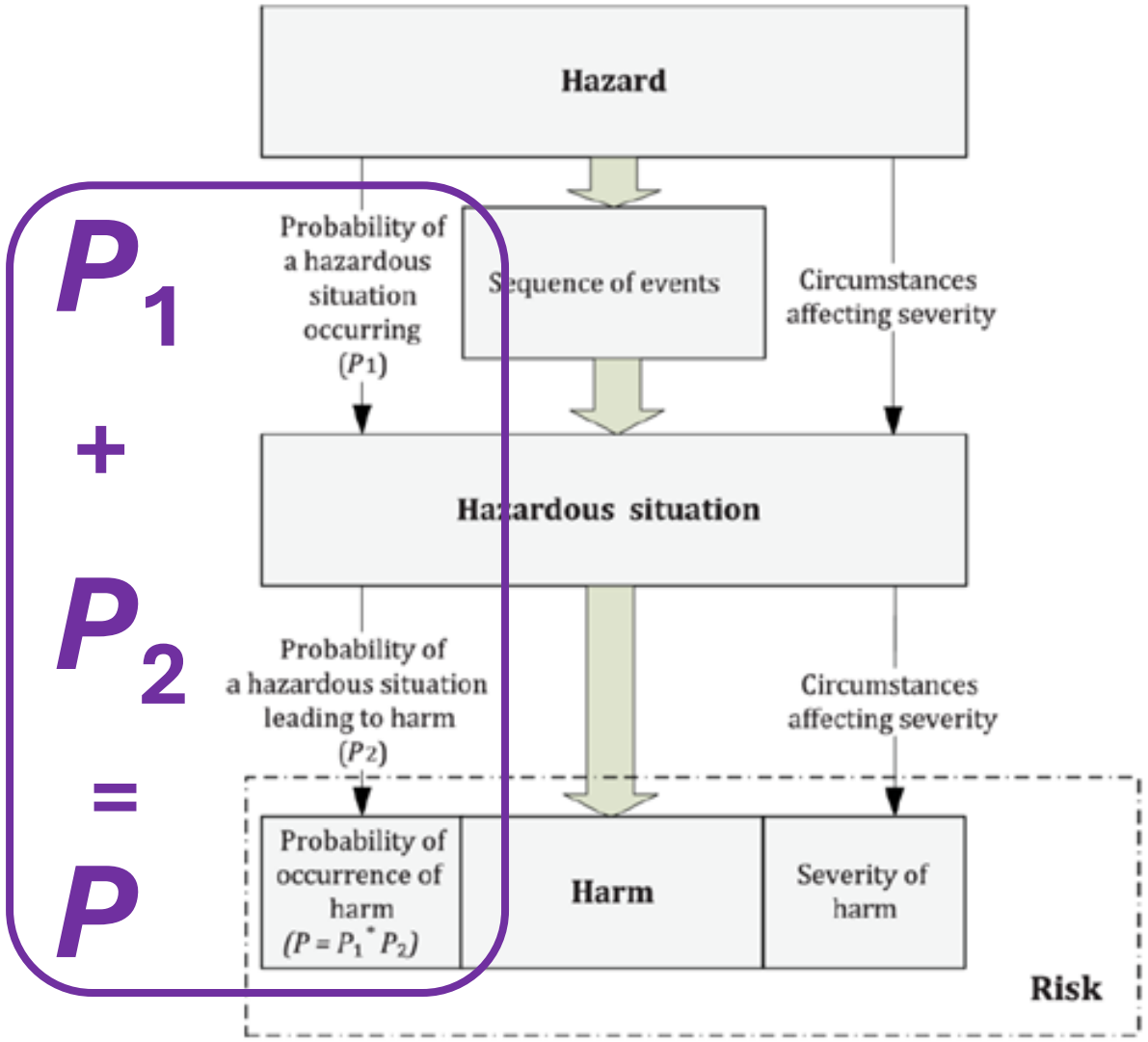
Identify & Evaluate Potential Harms for the IVD

- **Like non-IVD devices, manufacturers should consider having a medical or clinical expert participate in identifying potential harms and evaluating the severity level for the harms.**
- **Based on the IVD's intended use, consider:**
  - How critical is this test result in determining therapy for the related condition?
    - What harms may occur from misdiagnosis or inappropriate therapy?
  - If the test detects infectious disease, could an incorrect result affect spread to others/public health?
  - Does test detect/diagnose a treatable disease that if not detected could allow disease progression?
  - Does test predict therapy effectiveness such that a false result could affect therapy benefits?
  - Does test screen blood or tissue to ensure safe & compatible transfusion or donation?
  - If medical intervention occurred, would the outcome be reversible?
  - Does the IVD connect to a network or internet such that patient data could be modified or stolen?

Estimation of Probability of Occurrence of Harm

P_1 x P_2 Approach

- **Probability of a patient being harmed = combined probability of each event in the sequence of events associated with a particular hazard and the potential harm.**
- **Given the complexity of IVDs and their indirect patient impact, consider the P_1 x P_2 approach to estimate probability to ensure analysis is performed by persons with appropriate expertise, where:**
  - P_1 is the probability that the hazardous situation would occur; and
  - P_2 is the probability that a specific harm would result from that hazardous situation



ISO 14971:2019, Figure C.1 — Pictorial example of the relationship between hazard, sequence of events, hazardous situation and harm (from ISO/IEC Guide 63:2019)

Estimation of Probability of Occurrence of Harm

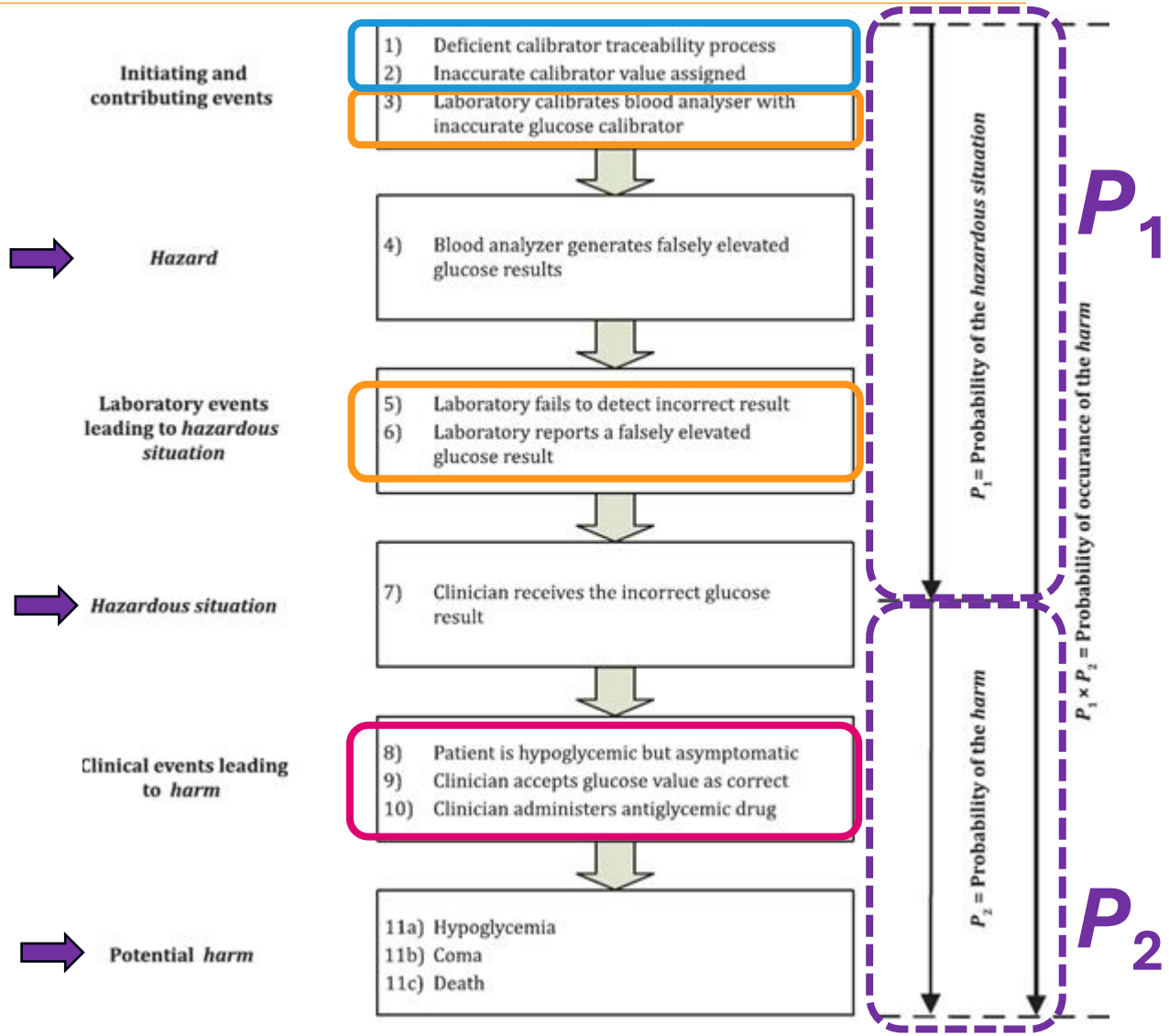
P_1 x P_2 Approach

- **Device: blood analyzer performing glucose measurements in a medical laboratory**
- **P_1 = probability of occurrence of the hazardous situation**
  - Team estimating P_1 should be familiar with design/construction, use, and servicing of IVD and understand use environment
- **P_2 = probability of harm occurring from a hazardous situation**
  - Team estimating P_2 should be familiar with medical use of the IVD results

Events controlled by manufacturer.

Events beyond manufacturer's control but potentially controlled by information accompanying device (e.g., IFU).

Events beyond laboratory's direct control.



ISO/TR 24971:2020, Figure H.1 — Illustration of the sequence of events for a laboratory scenario involving an incorrect glucose measurement from an IVD medical device

Summary

IVDs: Special Risk Considerations Summary

- **Risk Management Process for IVDs**
  - Same as non-IVDs but use a different perspective for risk analysis inputs.
- **IVD Overview**
  - Key difference for IVDs = indirect patient impact (may be difficult to evaluate)
- **Known and Foreseeable Hazards and Hazardous Situations for IVDs**
  - Typical non-IVD device hazards mostly apply to non-patient operators; may also be components of hazardous situations
  - Primary IVD patient hazards:
    - An **incorrect test result** *(false positive/negative from a qualitative test; or false increased/ decreased value from a quantitative test)*
    - A **delayed test result**, or
    - **Incorrect information accompanying a test result**

IVDs: Special Risk Considerations Summary (cont'd)

- **Identify Hazards & Hazardous Situations Related to Intended Use & Device Description for IVDs**
  - ISO/TR 24971:2020, Annex H provides useful guidance to help identify additional hazardous situations that could lead to these IVD patient hazards based on the device's intended use and description.
- **Identify & Evaluate Potential Harms for IVDs**
  - Manufacturers may find it more efficient to use a P_1 x P_2 approach to allow for different groups of experts to evaluate the risk components with which they are most familiar. Then, combine the scores from the segmented analyses to get the overall probability of occurrence of harm for each risk.

Questions?

.....of sharing knowledge

Thank you for your attention

Christie Hughes, MPH, MLS(ASCP), RCC-IVDR

Principal Consultant, Qserve Group

USC Mann

Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences

Drug-Device Combination Products Evaluation and Risk Assessment

APEC Symposium

September 16, 2024

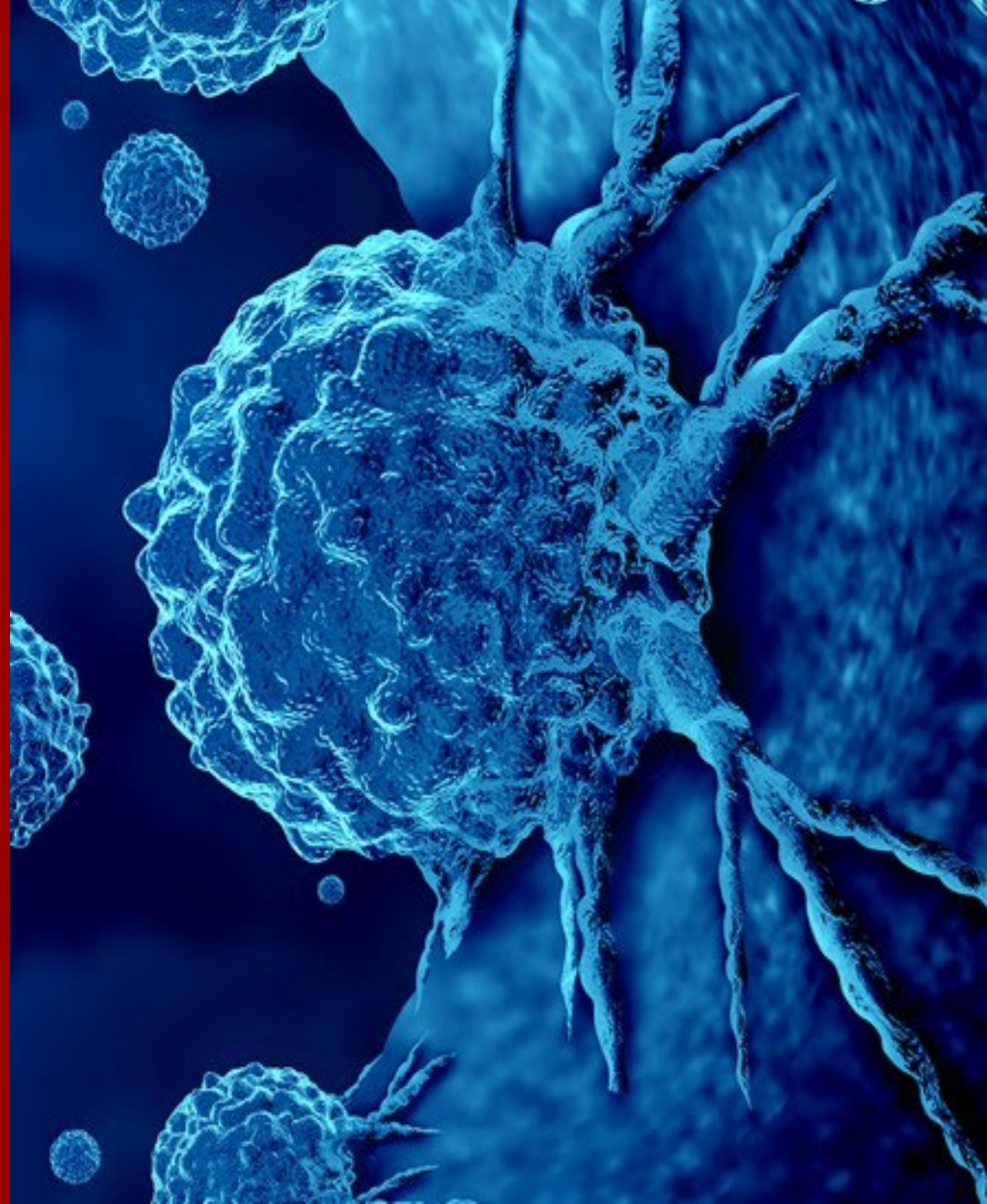
James Wabby

Head, Global Regulatory Affairs

Combination Products and Emerging Technologies

Volwiler Senior Research Fellow – Regulatory Science

AbbVie, Inc.



Combination Product Evaluation Overview

Agenda
Introduction
Evolution of Drug Delivery
Future Industry Portfolio
Complex Product Development
• QMS Landscape • Asset Characterization Evaluation • Risk and Usability Modeling Introduction • Key Deliverable: Upfront Development Planning • Discussion

Preparing For The Next Generation of Products

> An organization's ability to learn, and translate that learning into action rapidly, is the ultimate competitive advantage.

Jack Welch

former CEO and Chairman of General Electric

Definition of Combination Products

Combination products are therapeutic, aesthetic, and diagnostic products that combine drugs, devices, and/or biological products.

Evolution of Drug Delivery

Infusion IV

Vials

Prefilled Syringe

Needle Safety Device

Autoinjector

Large Volume Injector

Ease of Use | Reduce Overfill

Patient safety | Regulatory

Adherence | competition | patient

Patent | Vol/Visc. | Patient (IV-SC)

The global precision medicine market in terms of revenue was estimated to be worth $29.1 billion in 2023 and is poised to reach $50.2 billion by 2028, growing at a CAGR of 11.5% from 2023 to 2028.[2]

Combination Products Market is presumed to reach the market size of nearly USD 296.74 Billion by 2032 from USD 144.66 Billion in 2023 with a CAGR of 8.31% under the study period 2024-2032.[1]

[1] Drug Device Combination Products Market Share & Growth Report (valuemarketresearch.com)

[2] Precision Medicine Market Size, Share, Trends and Revenue Forecast [Latest] (marketsandmarkets.com)

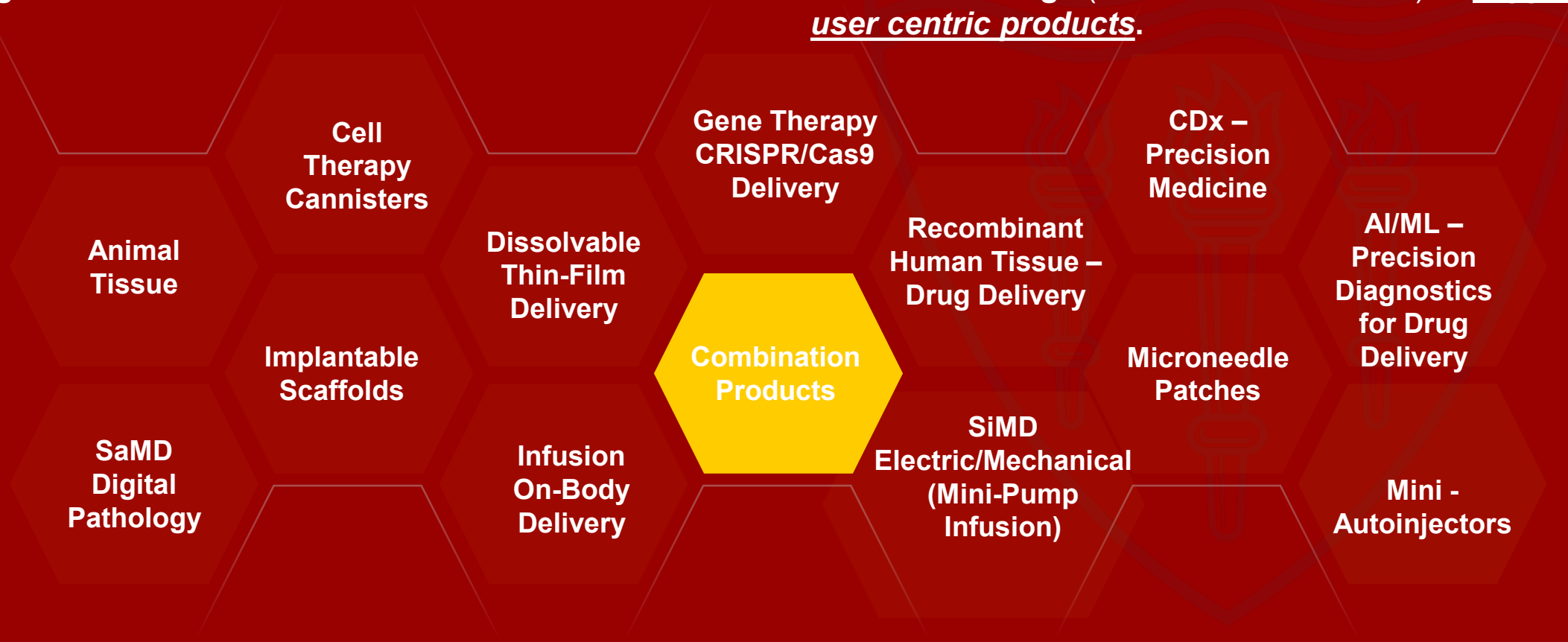
Nanotherapeutics: Future Industry Portfolio

Disruptive Medicine Innovation

Combining precision diagnostics and precision therapeutic/aesthetic products for unmet medical needs and next generational needs - product lifecycle management.

Future Product Strategy

Being able to construct, fabricate, regulate, and combine therapeutic and/or aesthetic biopharma products and **devices through material science application with a size in the nano-range** (at least one dimension) **to *support user centric products***.



Complex Product Development Overview

Device development integrated with medicinal development across the lifecycle…

Medicinal	**Discovery**		**Development**	**Launch**	**LCM**
Device	**Concept**	**Feasibility & Development**	**Validation**	**Launch**	**LCM**

Current Problem: Pre-launch device development happens within **'Development'** phase of medicinal development, **but the vision is for it to start much sooner integrated with medicinal development. Overall: Fragmented and Siloed Deliverables**

…for all device technologies in all Therapeutic Areas

Example Device Technologies

- Combination Products
- Standalone Devices
- Digital Health Tools (e.g., AI/ML)
- Diagnostic Devices (e.g.,CDx)

Therapeutic Areas

- Immunology
- Oncology
- Neuroscience
- Ophthalmology
- Cardiovascular
- Other Specialty Products

Regulatory Vision

Combination products

Address high priority issues with combination products while evaluating future state strategies with **an "Enterprise Integrated Mindset"**

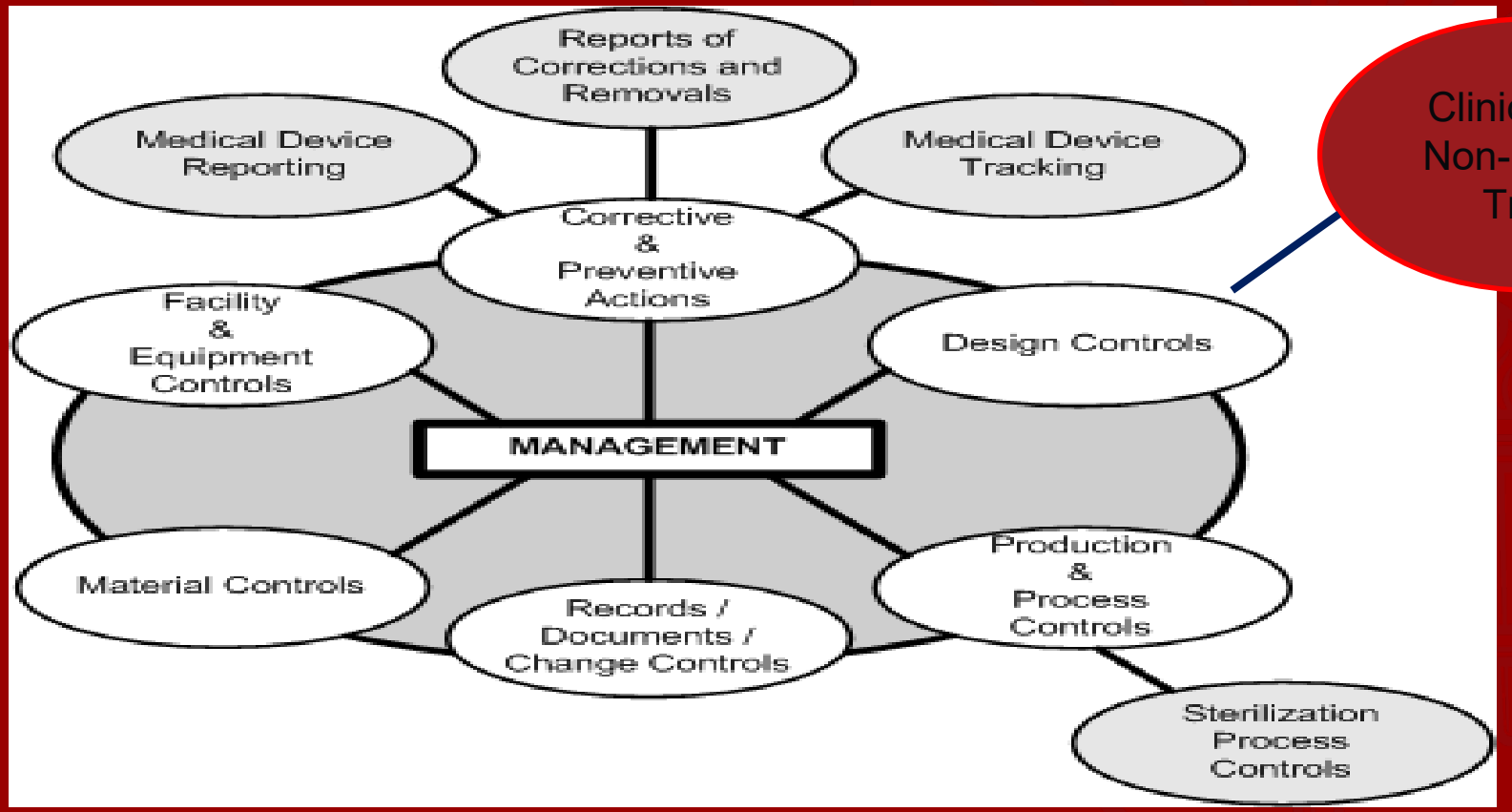
Major markets

Evaluate strategies with a primary focus on core markets and other markets - Document the Integrated Regulatory Strategy upfront for the whole asset.

Quality Management System

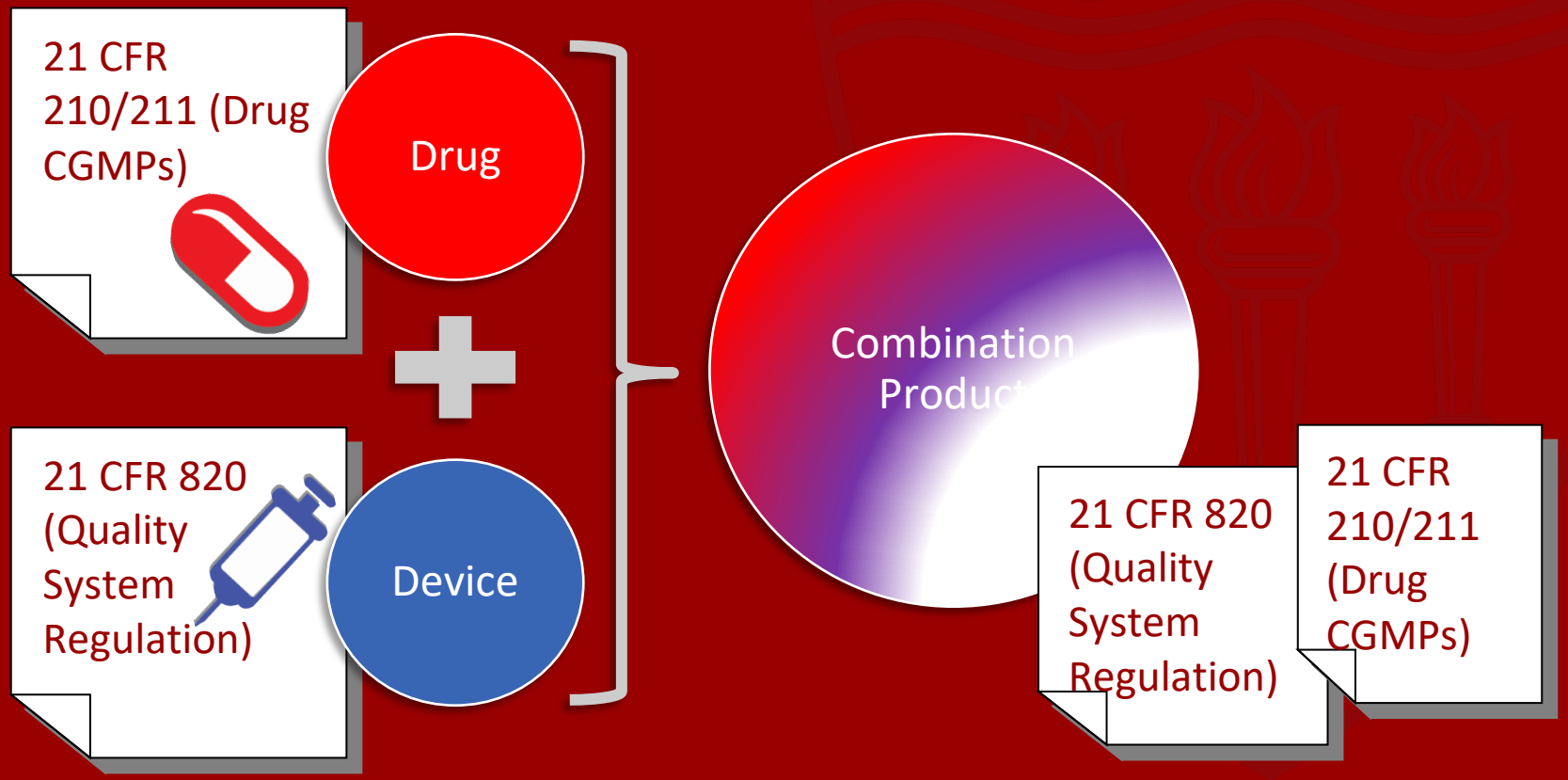
Clinical and Non-Clinical Trials

Quality Management System



Characterization and GMP Regulations

- Industry needs to determined how is the asset characterized when combining drugs, devices, companion diagnostics, and biologics, each retains its "regulatory identity" in the final product.



Characterization of Combination Products

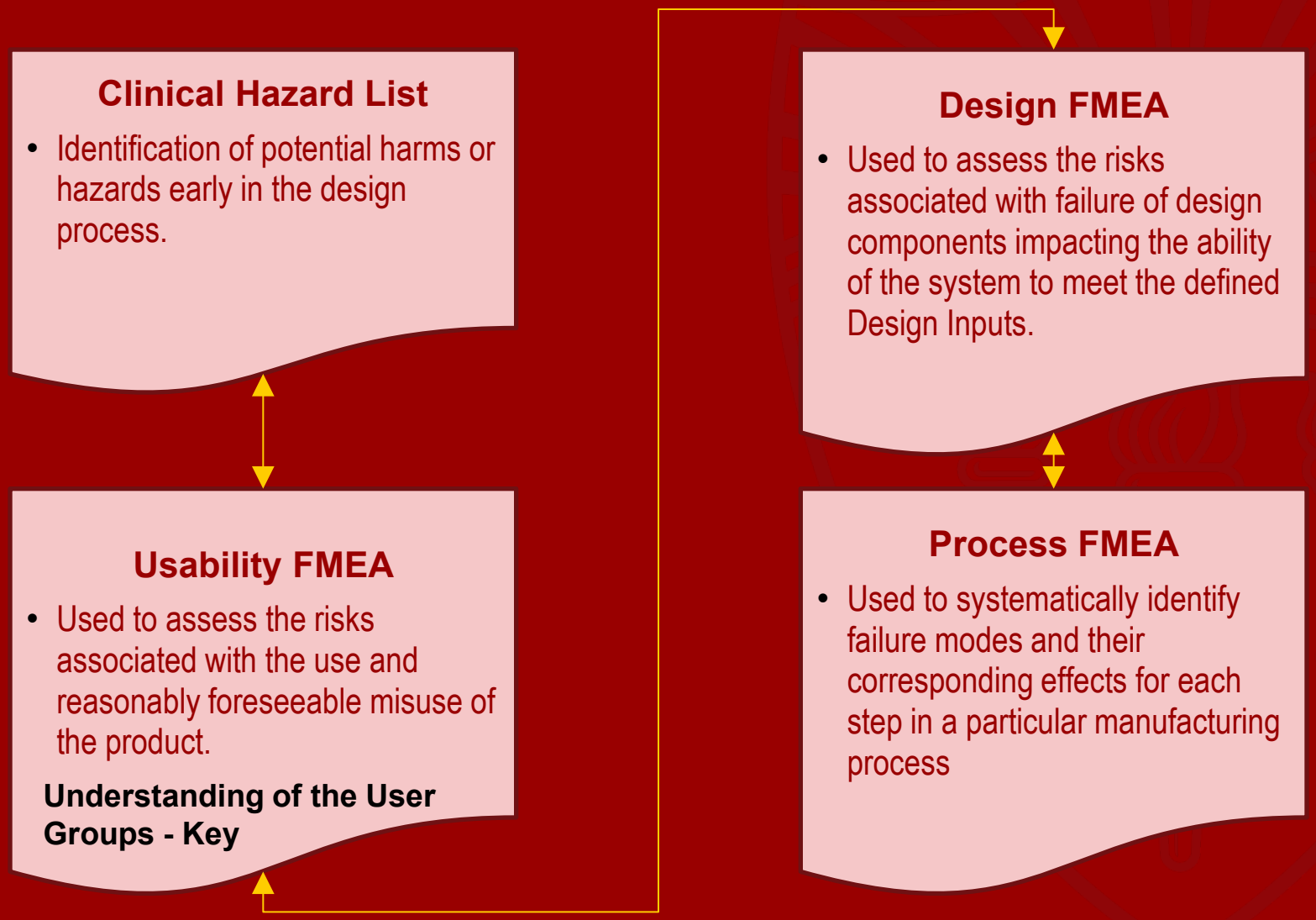
Characterization	Example
Single Entity Physically/chemically combined in a single entity	• Drug-coated device, pre-filled syringe or dermal filler with lidocaine
Co-packaged A package containing separate items	• Surgical kit with gloves, catheter, and anesthetic jelly • Drug or biological product packaged with an applicator, empty syringe, or injector pen
Cross-labeled Entirely separate items that are specifically labeled for use together	• Drug and auto injector (labeled for use together) or with a companion diagnostic (CDx)
Convenience Kit Device and drug/biologic agent are packaged together **and used "As-Is"** (Independently Marketed)	• Filter needle packaged with drug/biologic agent • **A manufacturer of a "convenience kit" has no cGMP requirements beyond those that apply to the assembly, packaging, labeling or sterilization of the kit. The final rule's new requirements do apply [if] any of the kit's components is repackaged, relabeled or otherwise modified to be included in the kit.**

Risk Management Within Combination Product Development

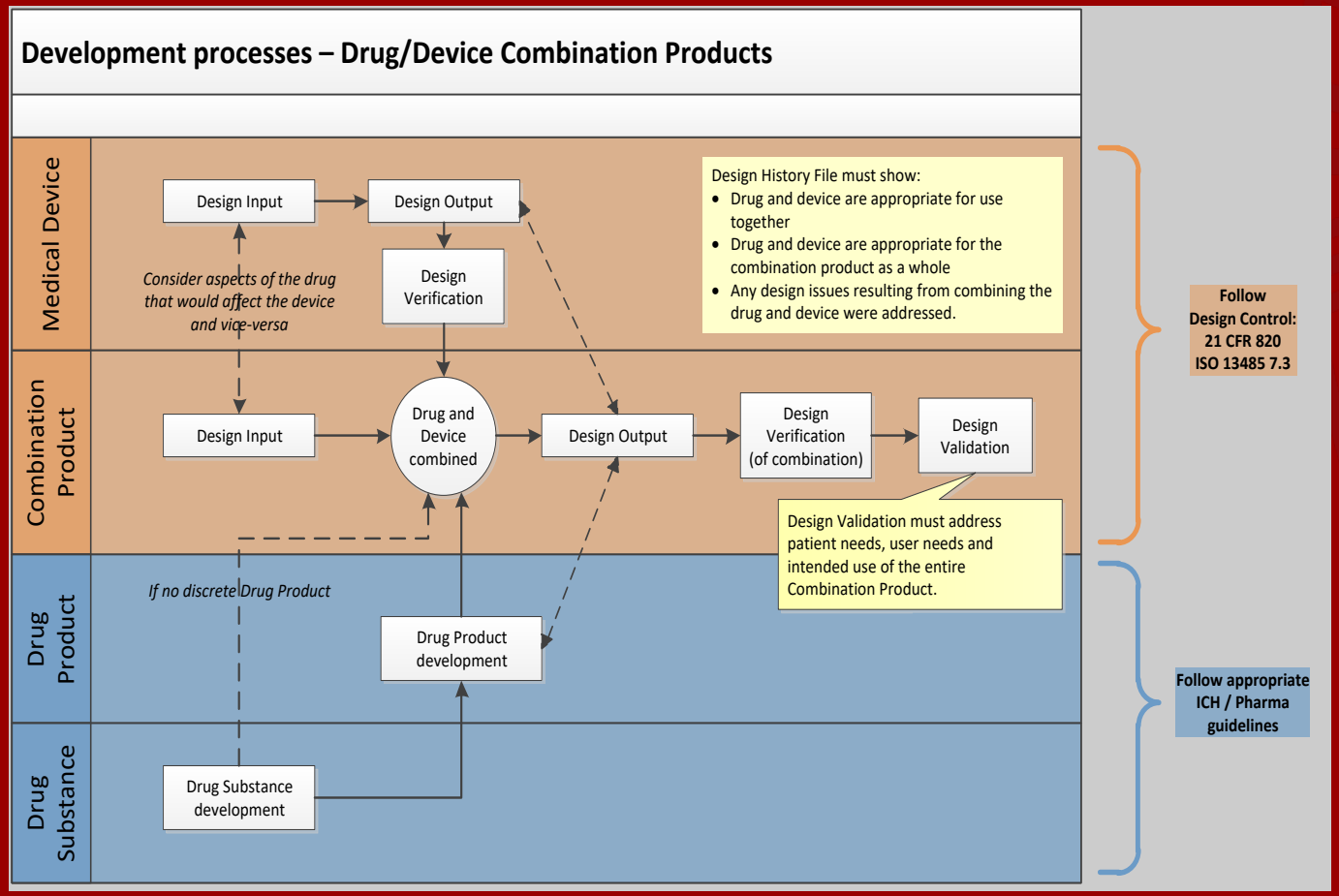
Concept	Feasibility	Development	Validation	Launch Readiness	Launch
N/A	Risk Management Plan	Risk Management Plan	Risk Management Plan	Risk Management Plan	Annual Risk Management File Review
	Clinical Hazards List	Clinical Hazards List	Clinical Hazards List	Clinical Hazards List	
	Design FMEA	Design FMEA	Design FMEA	Design FMEA	
	Usability FMEA	Usability FMEA	Usability FMEA	Usability FMEA	
	Process FMEA	Process FMEA	Process FMEA	Process FMEA	
			Risk Mgmt Report	Risk Mgmt Report	
			Risk Benefit Analysis	Risk Benefit Analysis	

Consider starting the characterization of the combination asset as soon as possible, especially for novel products to be able to develop a Risk Management Model.

Combination Product Risk Analysis Overview



Overall : Early Product Development Planning is Critical



Early Development Planning is a MUST:

- **Strategic Partnerships - growing investments;**
- **Intellectual Property Initiatives - competitive market dynamics;**
- **Product Development Approaches;**
  - **Clinical Strategy**
  - **Platform Technologies**
  - **EDDOs**
- **Quality and Risk Management Systems Optimizations; and**
- **Regulatory Submission Market Plans**
- **HTA/Reimbursement Landscaping**

Integrated Regulatory Strategy

USC

Discussion

AI and Its Use in Medical Devices

Mitigating Novel Risks

September 16, 2024

Bridging Consulting LLC

REGULATORY · QUALITY · CLINICAL

Yu Zhao
President & Principal Advisor
Bridging Consulting LLC

AGENDA

Bridging Consulting LLC

- Uses of AI in Medical Devices
- Novel Risks Associated with Using AI in Medical Devices
- Risk Control and Mitigation Strategies
- Case Studies
- Summary

Use of AI in Medical Devices

Artificial Intelligence

Types of AI Technologies

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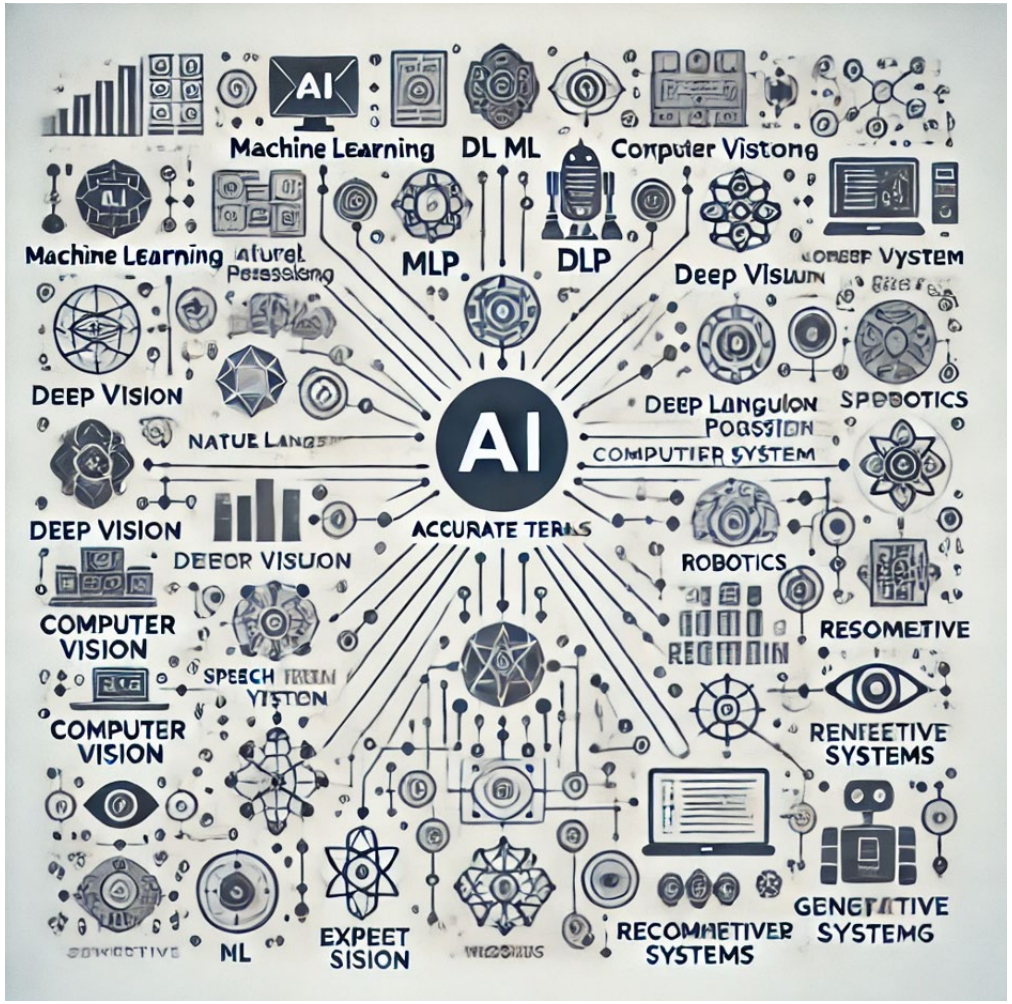

Source: DALL-E 3, OpenAI.

- Machine learning (ML)
  - Deep learning (DL)
  - Locked algorithm, adaptive algorithm
- Natural language processing (NLP)
- Computer vision (CV)
- Expert system
- Speech recognition
- Generative AI
  - Large language model (LLM)

Machine Learning vs. Deep Learning

Same or Different?

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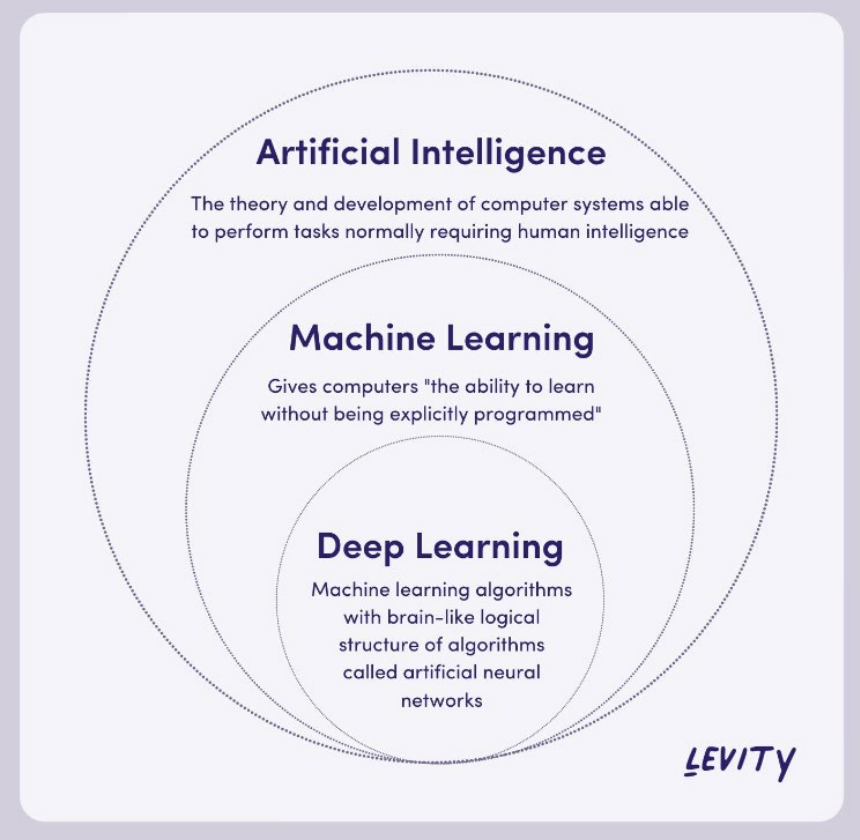

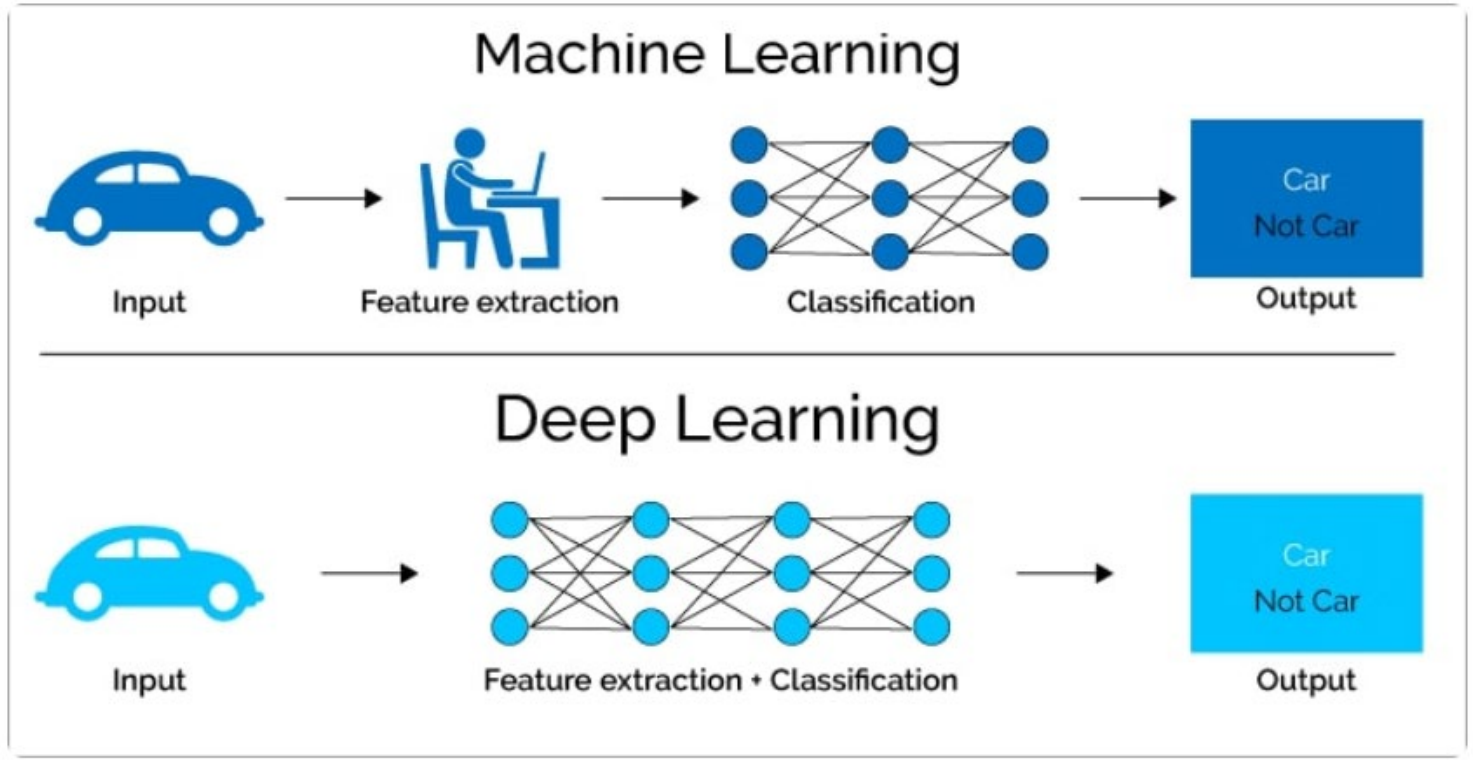

The Deep Learning algorithm doesn't need a software engineer to identify features but is capable of automatic feature engineering through its neural network. (Source: softwaretestinghelp.com)

Source: https://levity.ai/blog/difference-machine-learning-deep-learning.

FDA AI/ML-Enabled Device List

N=950 in August 2024

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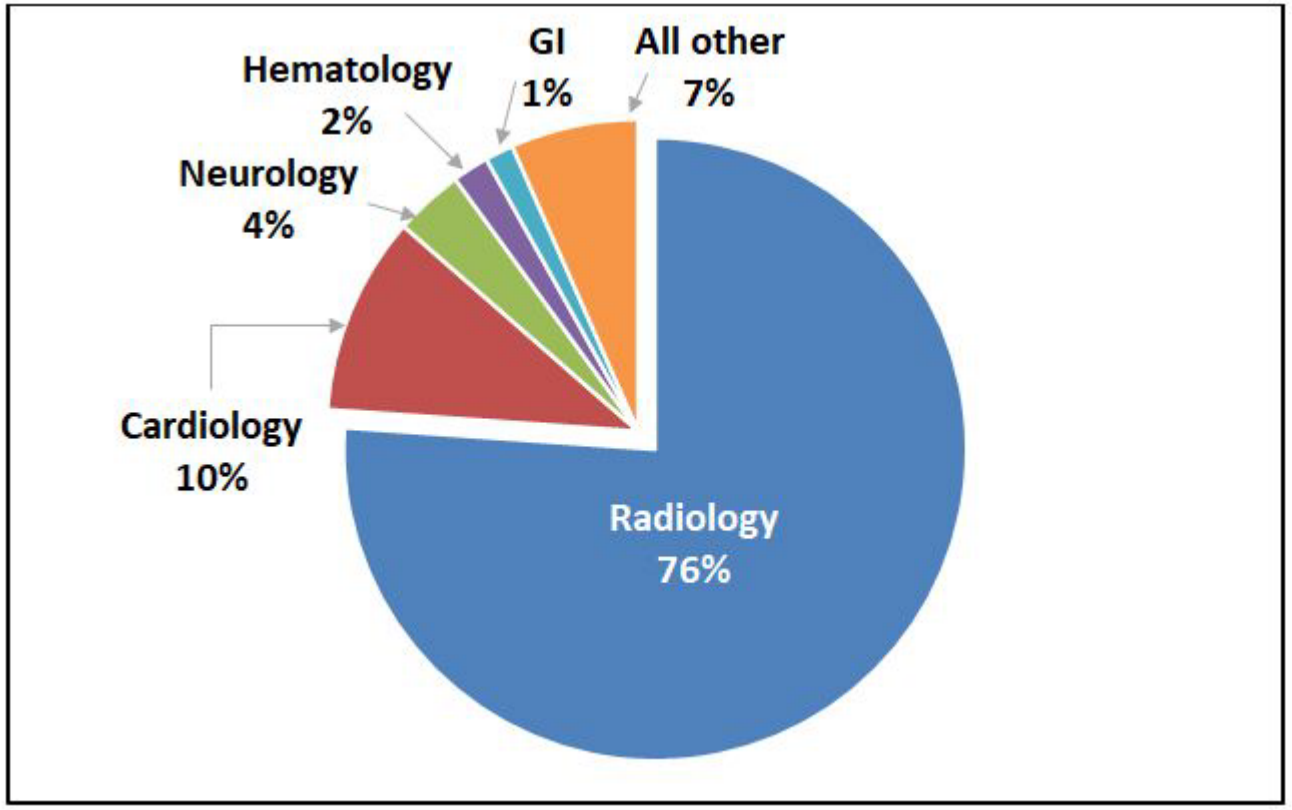

Medical Specialty	Top 3 Product Codes	% of category total	Regulation #	Generic Device Name
Radiology	LLZ	20%	892.2050	System, Image Processing, Radiological
	QIH	17%	892.2050	Automated Radiological Image Processing Software
	JAK	10%	892.1750	System, X-Ray, Tomography, Computed
Cardiovascular	DQK	17%	870.1425	Computer, Diagnostic, Programmable
	DQD	7%	870.1875	Stethoscope, Electronic
	PJA	7%	870.1415	Coronary Vascular Physiologic Simulation Software
Neurology	HAW	15%	882.4560	Neurological Stereotaxic Instrument
	OLZ	15%	882.1400	Automatic Event Detection Software For Polysomnograph With Electroencephalograph
	QEA	12%	882.1455	Brain Injury Adjunctive Interpretive Oculomotor Assessment Aid

Source: https://www.linkedin.com/feed/update/urn:li:activity:7227133349733068801/ by Naveen Agarwal, Ph.D., August 14, 2024.

AI/ML-Enabled Devices

Sample Applications

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- Radiology:
  - Imaging processing and analysis
- Cardiology:
  - Analyzing EEGs and detecting abnormalities
- Pathology:
  - Analyzing tissue samples and detecting cancerous cells
- Neurology:
  - Analyzing EEGs and brain scans, detecting and monitoring neurological disorders
- Oncology:
  - Analyzing genetics, imaging, etc., to suggest personalized treatment plans
- Orthopedics:
  - Assisting in surgical planning based on imaging and providing guidance
- Surgeries:
  - Remote viewing and operating robotics
- Respiratory:
  - Remote monitoring and real-time detection

Image Sources: https://www.tcdmd.com; https://www.itnonline.com/.

AI/ML-Enabled Devices

Intended Uses

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- Assistive
  - Helping perform tasks faster without changing existing workflows
  - Computer-Assisted Triage (CADt): ContaCT (DEN170073)
  - Computer-Assisted Detection (CADd): GI Genius (DEN200055)
  - Computer-Assisted Diagnosis (CADx): QuantX (DEN170022)
- Augmented
  - Modifying/enhancing current workflows, helping make better decisions
  - E.g., Caption Guidance (DEN190040)
- Autonomous
  - Replacing current workflow by automating decision-making process
  - E.g., IDx-DR (DEN180001)
- Digital therapeutics (DTx)
  - Providing cognitive behavioral therapies (CBTs)
  - E.g., reSET (DEN160018), EaseVRx (DEN210014)

Novel Risks Associated with Using AI in MDs

Novel Risks Associated With AIs

General Risks

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- Human-AI interaction risks
- Inaccurate results
- User over-reliance
- Cybersecurity vulnerabilities
- Inadequate data privacy and confidentiality
- Unclear accountability and liability
- Inadequate training and education

Novel Risks Associated With AIs

Machine Learning & Deep Learning

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- Data bias and discrimination
- Poor generalization
- Overfitting & underfitting
- Lack of model interpretability
- Inadequate validation without an established ground truth
- Model drift
- Input data changes
- Clinical practice changes

Novel Risks Associated With AIs

Large Language Model

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- Contextual misunderstanding
- Hallucination
- Data bias and discrimination
- Lack of explainability
- Inconsistent outputs
- Complex query handling
- Validation difficulties
- Cultural or situational insensitivity
- Transparency concerns

Novel Risks Associated With AIs

Digital Therapeutics (DTx)

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- Poor user engagement and adherence
- Poor usability
- Lack of accessibility
- Psychological and behavioral risks
- Virtual Reality (VR) headset:
  - Motion sickness
  - Eye strain and fatigue
  - Neck and shoulder strain
  - Derealization and depersonalization
  - Excessive visual stimuli

Risk Control and Mitigation Strategies

Risk Control and Mitigation Strategies

Overall Approach for AI/ML-Enabled Medical Devices

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- Existing risk-based regulatory scheme works
- Existing risk management process works
  - There are new types of hazards, requiring new risk control measures
- It's necessary to standardize terminologies and establish guiding principles
- It's helpful to use harmonized standards, regulations, guidance to align expectations and drive consistencies

Risk Control and Mitigation Strategies

Standards and Regulations

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- Standards
  - ISO 14971:2019: Medical devices — Application of risk management to medical devices
  - ISO 24971:2020: Medical devices — Guidance on the application of ISO 14971
  - AAMI CR34971:2022: Guidance on the Application of ISO 14971 to Artificial Intelligence and Machine Learning
  - ISO/CD TS 24971-2: (committee draft) Medical devices — Guidance on the application of ISO 14971Part 2: Machine learning in artificial intelligence
  - ISO 62304:2006: Medical device software — Software life cycle processes
  - IEC TR 24028:2020: Information technology — Artificial intelligence — Overview of trustworthiness in artificial intelligence
  - IEC 81001-5-1:2021: Health software and health IT systems safety, effectiveness and security, Part 5-1: Security — Activities in the product life cycle
  - ISO 27701:2019: Security techniques — Extension to ISO/IEC 27001 and ISO/IEC 27002 for privacy information management — Requirements and guidelines
  - NIST SP 800-53: Security and Privacy Controls for Information Systems and Organizations
- Laws and regulations
  - EU AI Act: Regulation (EU) 2024/1689: Artificial Intelligence Act
  - EU GDPR: Regulation (EU) 2016/679: General Data Protection Regulation

Risk Control and Mitigation Strategies

Guidance and Whitepaper

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- U.S. FDA
  - Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions — Final Guidance (Sep 27, 2023)
  - Content of Premarket Submissions for Device Software Functions – Final Guidance (Jun 14, 2023)
  - Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data in Premarket Notification (510(k)) Submissions – Final Guidance (Sep 28, 2022)
  - Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan (Jan 2021)
  - Good Machine Learning Practices for Medical Device Development: Guiding Principles (Oct 2021) – U.S. FDA, Health Canada and UK MHRA
  - Transparency for Machine Learning-Enabled Medical Devices: Guiding Principles (Jun 2024) – U.S. FDA, Health Canada and UK MHRA
- International Medical Device Regulators Forum (IMDRF)
  - Machine Learning-enabled Medical Devices: Key Terms and Definitions (May 6, 2022)
  - SaMD: Possible Framework for Risk Categorization and Corresponding Considerations (Sep 2014)
  - SaMD: Application of Quality Management System (Oct 2015)

Risks and Mitigations

General Risks

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- Human-AI interaction risks
  - Improving usability designs, formative and summative HF testing
- Inaccurate results
  - Verification and validation testing, real-world performance monitoring
- User over-reliance
  - User training and education to understand device capabilities and limitations
  - "human-in-the-loop"
- Cybersecurity vulnerabilities
  - Security design, testing, monitoring and updates
- Inadequate data privacy and confidentiality
  - Robust design, i.e., access control, clear identification of personal sensitive information, deidentification, transparency
- Unclear accountability and liability
  - Accountability framework, thorough documentation of decision-making process
- Inadequate training and education
  - Develop and deliver user-appropriate training

Risks and Mitigations

Machine Learning & Deep Learning

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- Data bias and discrimination
  - Representative model training dataset, data management, validation testing
- Poor generalization
  - Representative model training dataset, adequate validation testing
- Overfitting & underfitting
  - Reduce/increase ML model complexity, regularization/de-regularization, feature engineering
- Model interpretability
  - Using tools such as SHAP and LIME, model transparency, model simplification
- Inadequate validation without an established ground truth
  - Establish new ground truth or surrogate reference value
- Model drift / Input data changes / Clinical practice changes
  - Monitor model performance, conduct market intelligence, perform periodic retraining

Novel Risks Associated With AIs

Large Language Model

Bridging Consulting LLC

- Contextual misunderstanding / Complex query handling
  - Prompt engineering, online help and user training
- Hallucination
  - Better model training datasets, real-time fact checking, retrieval augmentation, model retraining, reinforcement learning from human feedback
- Data bias and discrimination
  - Relevant, diverse and high-quality model training datasets,
- Lack of explainability
  - Explainable AI (XAI) approaches, including providing confidence levels or rationale
- Inconsistent outputs
  - Ensure correctness of outputs
- Validation difficulties
  - Cross-reference outputs with medical guidelines, human clinical expert evaluation
- Cultural or situational insensitivity
  - Train model on culturally diverse datasets, use emotional cues through prompts
- Transparency concerns
  - Proper user labeling disclosing the use of LLM

Novel Risks Associated With AIs

Digital Therapeutics (DTx)

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- Poor user engagement and adherence
  - Improve user interfaces encouraging active participation, with reminders and progress reports
- Poor usability
  - Apply user-centric designs, followed by formative and summative HF testing
- Lack of accessibility
  - Increase hardware/software compatibility, balance mobile vs. cloud computing
- Psychological and behavioral risks
  - Involve mental health experts in design and testing process, conduct user testing, perform postmarket surveillance
- Virtual Reality (VR) headset:
  - Motion sickness – limit session durations, offer user-controlled navigation options
  - Eye strain and fatigue – adjustable focus settings, incorporate regular breaks during session
  - Neck and shoulder strain – apply ergonomical design, conduct user testing, incorporate regular breaks
  - Derealization and depersonalization – limit session durations, provide clear transition between VR and real-world environments
  - Excessive visual stimuli – allow customization of sensory input levels, include environment options

Case Studies

CADx (Computer-Assisted Diagnosis)

DEN170022 QiantX

Bridging Consulting LLC

Sec. 892.2060 Radiological computer-assisted diagnostic software for lesions suspicious of cancer.

(a) *Identification.* A radiological computer-assisted diagnostic software for lesions suspicious of cancer is an image processing prescription device intended to aid in the characterization of lesions as suspicious for cancer identified on acquired medical images such as magnetic resonance, mammography, radiography, or computed tomography. The device characterizes lesions based on features or information extracted from the images and provides information about the lesion(s) to the user. Diagnostic and patient management decisions are made by the clinical user.

Identified Risks to Health	Mitigation Measures
Incorrect lesion(s) characterization leading to false positive results may result in incorrect patient management with possible adverse effects such as unnecessary treatment, unnecessary additional medical imaging and/or unnecessary additional diagnostic workup such as biopsy.	Certain design verification and validation activities identified in special control (1) Certain labeling information identified in special control (2)
Incorrect lesion(s) characterization leading to false negative results may lead to complications, including incorrect diagnosis and delay in disease management.	Certain design verification and validation activities identified in special control (1) Certain labeling information identified in special control (2)

Identified Risks to Health	Mitigation Measures
The device could be misused to analyze images from an unintended patient population or on images acquired with incompatible imaging hardware or incompatible image acquisition parameters, leading to inappropriate diagnostic information being displayed to the user.	Certain design verification and validation activities identified in special control (1) Certain labeling information identified in special control (2)
Device failure could lead to the absence of results, delay of results or incorrect results, which could likewise lead to inaccurate patient assessment.	Certain design verification and validation activities identified in special control (1) Certain labeling information identified in special control (2)

CADx (Computer-Assisted Diagnosis)

Special Controls

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1. Design verification and validation must include:
   i. A detailed description of the image analysis algorithms including, but not limited to, a detailed description of the algorithm inputs and outputs, each major component or block, and algorithm limitations.
   ii. A detailed description of pre-specified performance testing protocols and dataset(s) used to assess whether the device will improve reader performance as intended.
   iii. Results from performance testing protocols that demonstrate that the device improves reader performance in the intended use population when used in accordance with the instructions for use. The performance assessment must be based on appropriate diagnostic accuracy measures (e.g., receiver operator characteristic plot, sensitivity, specificity, predictive value, and diagnostic likelihood ratio). The test dataset must contain sufficient numbers of cases from important cohorts (e.g., subsets defined by clinically relevant confounders, effect modifiers, concomitant diseases, and subsets defined by image acquisition characteristics) such that the performance estimates and confidence intervals of the device for these individual subsets can be characterized for the intended use population and imaging equipment.
   iv. Standalone performance testing protocols and results of the device.
   v. Appropriate software documentation (e.g., device hazard analysis; software requirements specification document; software design specification document; traceability analysis; description of verification and validation activities including system level test protocol, pass/fail criteria, results, and cybersecurity).

2. Labeling must include:
   i. A detailed description of the patient population for which the device is indicated for use.
   ii. A detailed description of the intended reading protocol.
   iii. A detailed description of the intended user and recommended user training.
   iv. A detailed description of the device inputs and outputs.
   v. A detailed description of compatible imaging hardware and imaging protocols.
   vi. Warnings, precautions, and limitations, including situations in which the device may fail or may not operate at its expected performance level (e.g., poor image quality or for certain subpopulations), as applicable.
   vii. Detailed instructions for use.
   viii. A detailed summary of the performance testing, including: test methods, dataset characteristics, results, and a summary of sub-analyses on case distributions stratified by relevant confounders (e.g., lesion and organ characteristics, disease stages, and imaging equipment).

Autonomous Diagnostic Devices

DEN180001 IDx-DR

Bridging Consulting LLC

Sec. 886.1100 Retinal diagnostic software device.

(a) *Identification.* A retinal diagnostic software device is a prescription software device that incorporates an adaptive algorithm to evaluate ophthalmic images for diagnostic screening to identify retinal diseases or conditions.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risk	Mitigation Measures
False positive results leading to additional unnecessary medical procedures • Diagnostic algorithm failure • Software failure	Clinical performance testing; Software verification, validation, and hazard analysis; and Protocol for technical specification changes
False negative results leading to delay of further evaluation or treatment • Diagnostic algorithm failure • Software failure	Clinical performance testing Software verification, validation, and hazard analysis; Protocol for technical specification changes; and Labeling
Operator failure to provide images that meet input quality specifications	Labeling, Training, and Human factors validation testing

Autonomous Diagnostic Devices

Special Controls

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1. Software verification and validation documentation, based on a comprehensive hazard analysis, must fulfill the following:
   a. Software documentation must provide a full characterization of technical parameters of the software, including algorithm(s).
   b. Software documentation must describe the expected impact of applicable image acquisition hardware characteristics on performance and associated minimum specifications.
   c. Software documentation must include a cybersecurity vulnerability and management process to assure software functionality.
   d. Software documentation must include mitigation measures to manage failure of any subsystem components with respect to incorrect patient reports and operator failures.
2. Clinical performance data supporting the indications for use must be provided, including the following:
   a. Clinical performance testing must evaluate sensitivity, specificity, positive predictive value, and negative predictive value for each endpoint reported for the indicated disease or condition across the range of available device outcomes.
   b. Clinical performance testing must evaluate performance under anticipated conditions of use.
   c. Statistical methods must include the following:
      i. Where multiple samples from the same patient are used, statistical analysis must not assume statistical independence without adequate justification.
      ii. Statistical analysis must provide confidence intervals for each performance metric.
   d. Clinical data must evaluate the variability in output performance due to both the user and the image acquisition device used.
3. A training program with instructions on how to acquire and process quality images must be provided.
4. Human factors validation testing that evaluates the effect of the training program on user performance must be provided.
5. A protocol must be developed that describes the level of change in device technical specifications that could significantly affect the safety or effectiveness of the device.
6. Labeling must include:
   a. Instructions for use, including a description of how to obtain quality images and how device performance is affected by user interaction and user training.
   b. The type of imaging data used, what the device outputs to the user, and whether the output is qualitative or quantitative.
   c. Warnings regarding image acquisition factors that affect image quality.
   d. Warnings regarding interpretation of the provided outcomes, including:
      i. A warning that the device is not to be used to screen for the presence of diseases or conditions beyond its indicated uses.
      ii. A warning that the device provides a screening diagnosis only and that it is critical that the patient be advised to receive follow-up care.
      iii. A warning that the device does not treat the screened disease.
   e. A summary of the clinical performance of the device for each output, with confidence intervals.
   f. A summary of the clinical performance testing conducted with the device, including a description of the patient population and clinical environment under which it was evaluated.

Digital Therapeutics (DTx)

DEN160018 reSET

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Sec. 882.5801 Computerized behavioral therapy device for psychiatric disorders.

(a) *Identification.* A computerized behavioral therapy device for psychiatric disorders is a prescription only device intended to provide a computerized version of condition-specific behavioral therapy as an adjunct to clinician supervised outpatient treatment to patients with psychiatric conditions. The digital therapy is intended to provide patients access to therapy tools used during treatment sessions to improve recognized treatment outcomes.

Identified Risk	Mitigation Measures
Device provides ineffective treatment, leading to worsening condition	Clinical data Software verification, validation, and hazard analysis Labeling
Device software failure, leading to delayed access	Software verification, validation, and hazard analysis Labeling
Use error / improper device use	Labeling

Digital Therapeutics (DTx)

Special Controls

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1. Clinical data must be provided to fulfill the following:
    a. Describe a validated model of behavioral therapy for the psychiatric disorder; and
    b. Validate the model of behavioral therapy as implemented by the device.

2. Software must be described in detail in the software requirements specification (SRS) and software design specification (SDS). Software verification, validation, and hazard analysis must be performed. Software documentation must demonstrate that the device effectively implements the behavioral therapy model.

3. The following labeling must be provided:
    a. Patient and physician labeling must include instructions for use, including images that demonstrate how to interact with the device.
    b. Patient and physician labeling must list compatible devices.
    c. Patient and physician labeling must include a warning that the device is not intended for use as a standalone therapy.
    d. Patient and physician labeling must include a warning that the device does not represent a substitution for the patient's medication.
    e. Physician labeling must include a summary of the clinical testing with the device.

Summary

Summary

AI and Its Use in Medical Devices: Mitigating Novel Risks

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- The use of AI in medical devices is ubiquitous, primarily still in low to moderate risk applications
- It raises novel risks in data management, machine-human interaction and proper validation, etc.
- The existing regulatory schemes and risk management framework work well overall, however,
- New/updated regulations, standards and guidance will help align expectations and drive consistencies on ensuring safety, efficacy and performance of AI-enabled devices

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SCAN ME