Pre-market Activities

Dan O'Leary CBA, CQA, CQE, CRE, SSBB, CIRM
President
Ombu Enterprises, LLC
Dan@OmbuEnterprises.com
www.OmbuEnterprises.com

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Topics

- The Role of Pre-market Activities
- Clinical Evaluation (Plan and Report)
- Risk Management (Plan, File, and Report)
- Benefit-Risk Determination
- Indicators and Thresholds
- Exercise B1 – Indicator and Threshold Analysis
- Questions

Resources

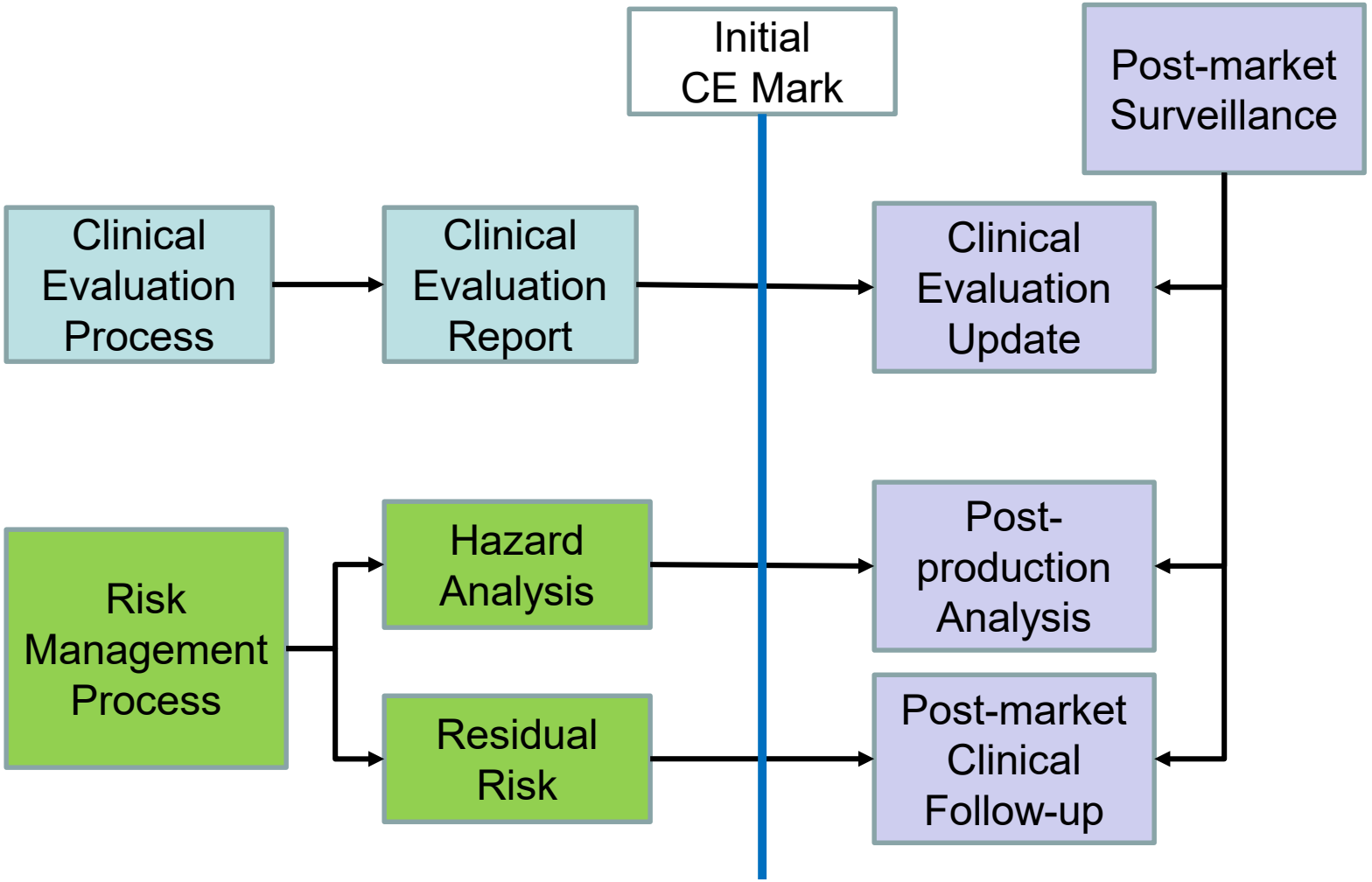
- The resources include:
  - A Clinical Evaluation Plan template
  - A description of the requirements and exceptions for Clinical Investigation
  - An Excel workbook to help determine if Clinical Investigation is required

The Role of Pre-market Activities

Pre-market

- There are many pre-market activities ranging from classification to implementing an appropriate QMS.
- Some of them create documentation and information that “initializes” post-market activities.
- Some post-market activities update the pre-market activities with new information.
- Complete the post-market activities before putting the CE Mark on the device!

Product Phases



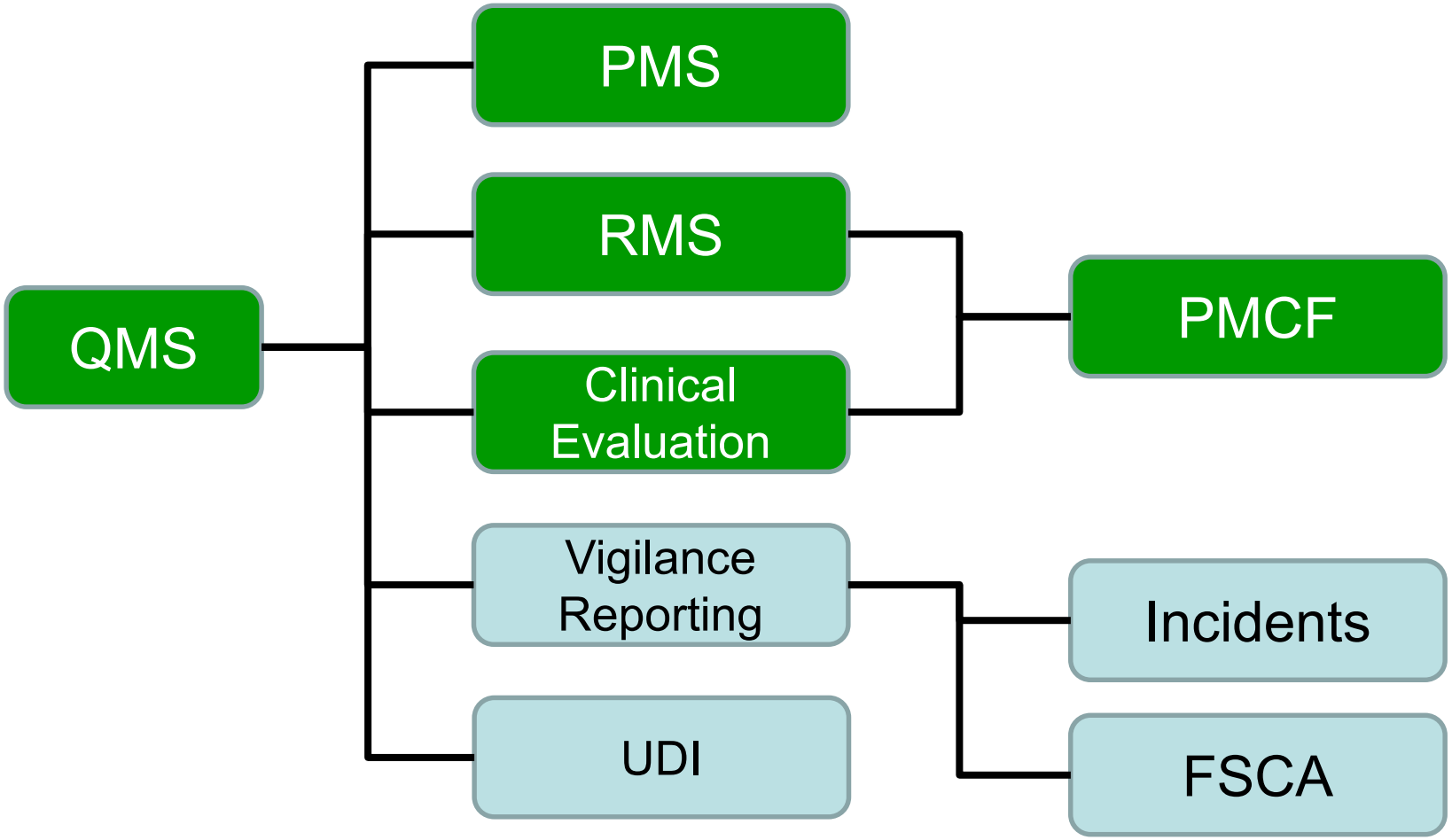
Before the CE Mark

- The list below is not comprehensive, but identifies some major activities to complete before applying the CE Mark to a medical device under the EU-MDR. The basis for the list is Article 10 General Obligations of Manufacturers
  - Classify the device (Annex VIII)
  - Determine the conformity assessment path (Assume Annex IX)
  - Demonstrate conformance with the General Safety And Performance Requirements (Annex I)
  - Conduct risk management (Annex I, Section 3)
  - Conduct Clinical Evaluation (Article 61 and Annex XIV)
  - Conduct Clinical Investigation as necessary (Article62 and Annex XV)
  - Prepare the technical documentation (Annex II)
  - Prepare the Technical Documentation on Post-market Surveillance (Annex III)
  - Identify the person responsible for regulatory compliance (Article 15)

After the CE Mark

- The list below is not comprehensive, but identifies some major activities to complete after applying the CE Mark to a medical device under the EU-MDR.
  - Implement the post-market market surveillance plan
  - Collect production information related to risk management
  - Collect post-production information related to risk management
  - Update the clinical evaluation
  - Conduct any indicated post-market clinical follow-up

The QMS


QMS
PMS
RMS
Clinical Evaluation
Vigilance Reporting
UDI
PMCF
Incidents
FSCA

Overall Structure

Overall Structure

Plan	Develop a plan for the activity. The EU-MDR usually has the required elements in the plan.
Do	Implement the elements of the plan. Keep records for use in preparing the report.
Report	Write a report that describes the plan's implementation, information learned, analysis, and conclusions.
Update	Update the report based on new information learned. The EU-MDR often lists the information sources and the update interval.
Submit	The EUMDR often lists the recipients, submission interval, and transmission method.

Overall Structure

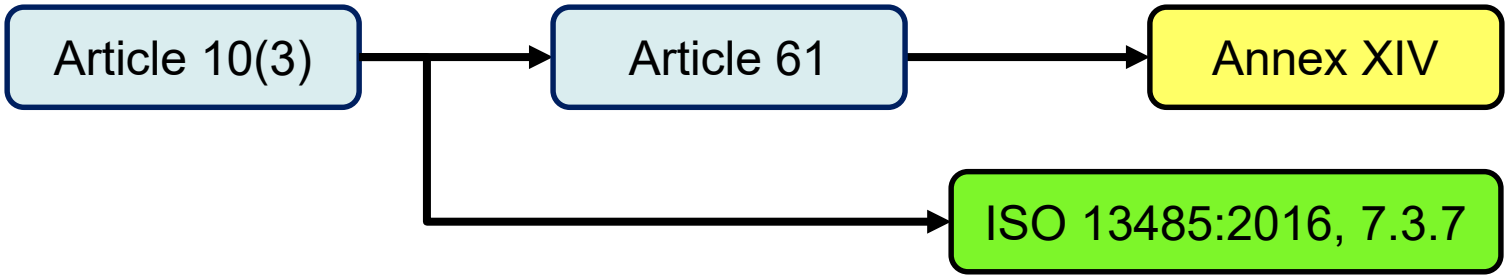
- The overall structure on the previous slide applies to both pre-market and post-market activities.
- It provides a convenient method to ensure procedures in this are have the required elements.
- Often the elements change based on the device class and other attributes such as implantable or sterile.
- For companies with a variety of classes and attributes, be sure you apply the structure to each specific device for each kind of plan/report.

Clinical Evaluation Overview

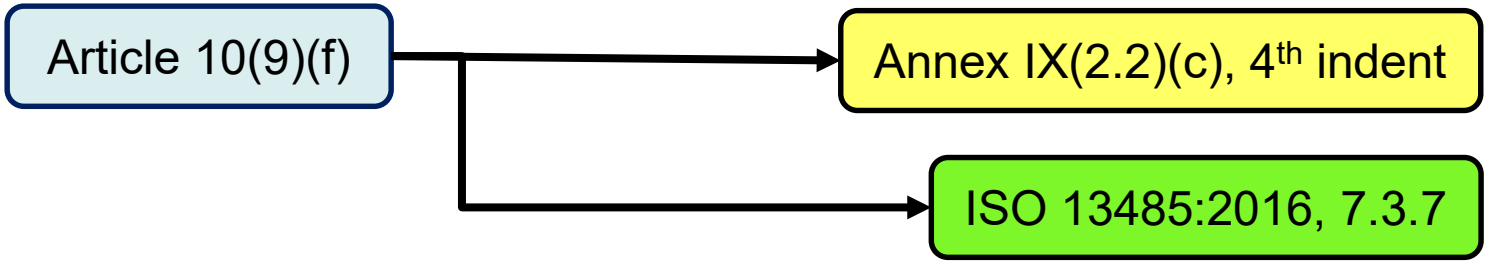
MEDDEV 2.7/1 Rev. 4

- MEDDEV 2.7/1 Rev.4 is applicable to the MDD, but not to the MDR.
- If, under the MDR you follow the MEDDEV you will be out of compliance
- The MEDDEV is good background reading on the clinical evaluation process

Clinical Evaluation



Clinical Evaluation as Part of the QMS



Definitions

- *Clinical Data* means information concerning safety or performance that is generated from the use of a device and is sourced from the following:
  - clinical investigations of the device concerned
  - clinical investigations or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated
  - reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated
  - clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up [Art 2(48)]

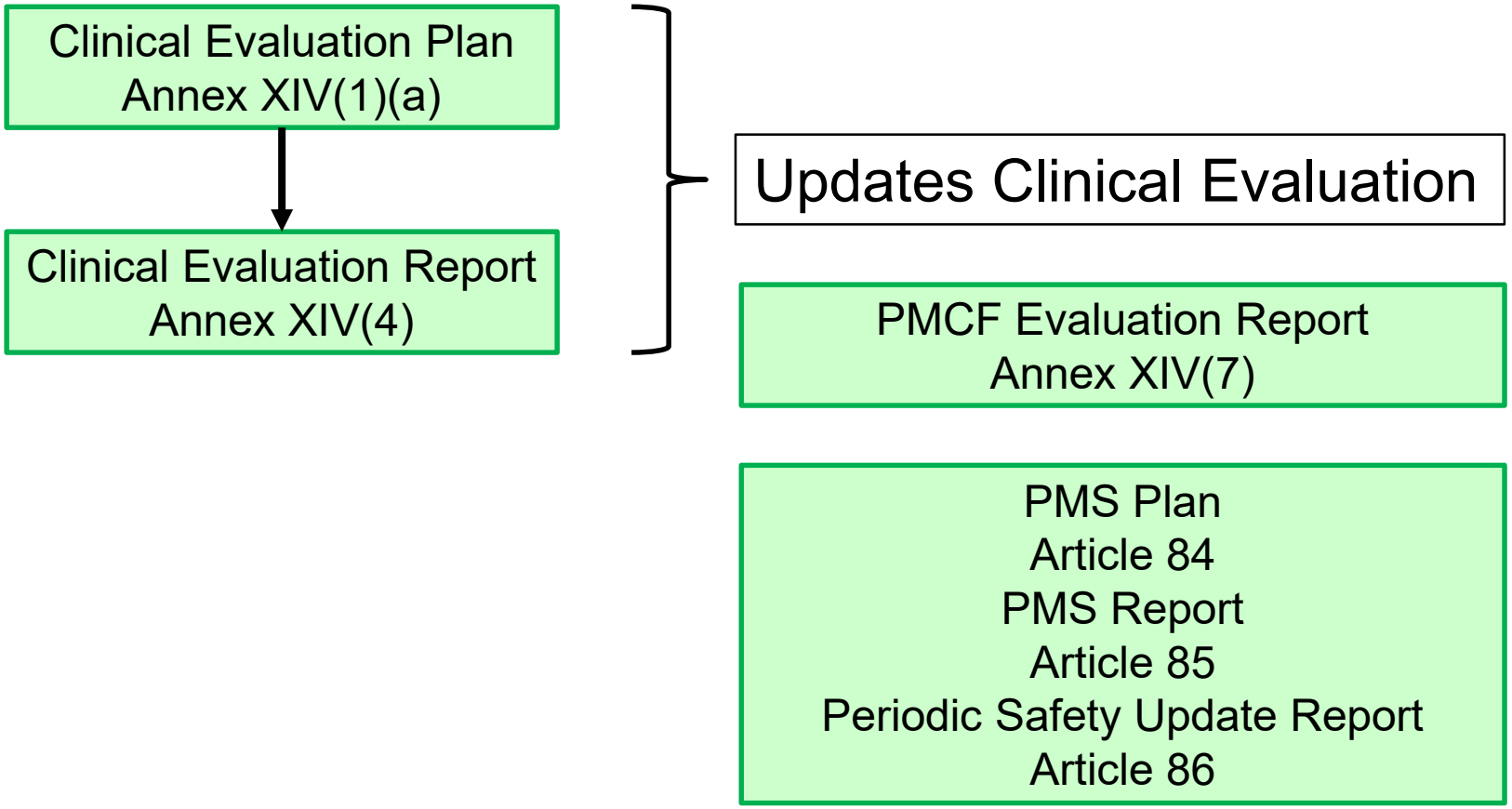
Definitions

- *Clinical Evaluation* means a systematic and planned process to continuously generate, collect, analyze, and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer [Art. 2(44)]

- *Clinical Benefit* means the positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome, including outcomes related to diagnosis, or a positive impact on patient management, or public health [Art. 2(53)]

- *Clinical Evidence* means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit, when used as intended by the manufacturer [Art. 2(51)]

Linkages


Clinical Evaluation Plan
Annex XIV(1)(a)
Clinical Evaluation Report
Annex XIV(4)
Updates Clinical Evaluation
PMCF Evaluation Report
Annex XIV(7)
PMS Plan
Article 84
PMS Report
Article 85
Periodic Safety Update Report
Article 86

Clinical Evaluation (Plan and Report)

Interested Parties

Authority Responsible for Notified Bodies

Article 45

Reviews, on a sampling basis, the NB's assessments of manufacturer's clinical evaluation documentation

Notified Body

Annex IX, Section 4.8

Assesses the manufacturer's clinical evaluation and prepares a Clinical Evaluation Assessment Report.

Manufacturer

Article 61 & Annex XIV Part A

Performs clinical evaluation following the Clinical Evaluation Plan and documents the results in the Clinical Evaluation Report.

Authority Responsible for Notified Bodies

- Article 45(1) includes the review of part of the MB monitoring
- The review includes the NB's assessment of the manufacturer's technical documentation
  - In particular review of Annex II, Section 6.1(c) and (d).
  - (c) Clinical evaluation plan, clinical evaluation report, & updates
  - (d) PMCF plan & PMCF evaluation report

- Article 45(2) says the sampling plan is representative of the types and risk of devices certified by the NB

Manufacturer's Overview

- Article 10
  - Section 3 requires a clinical evaluation in accordance with Article 61 and Annex XIV
  - Section 9(f) says that the QMS must address clinical evaluation
- Annex IX
  - Annex IX(2.2)(c) 4th indent says the application to the NB includes the procedures and techniques for clinical evaluation
- Article 61
  - Section 1 says the manufacturer plans, conducts, and documents a clinical following Annex XIX, Part A
- Annex XIV
  - Section 1(a) has the manufacturer establish and update a clinical evaluation plan with specified elements
  - Section 4 requires a clinical evaluation plan to document the results

Clinical Evaluation Plan

- The Annex XIV(1)(a) Clinical Evaluation Plan has some required information:
  - Identify the GS&PR that require support from clinical data
  - Specify the intended purpose of the device
  - Specify the intended target groups with clear indications and contra-indications
  - Provide a detailed description of the intended clinical benefits to patients
  - For clinical benefits specify clinical outcome parameters
  - Specify the methods to examine clinical safety, determine residual risks, and determine side-effects
  - Specify the parameters to determine the acceptability of the benefit-risk ratio
  - Describe how to address benefit-risk issues from specific components
  - A Clinical Development Plan

Plans Inside Plans

- The Clinical Evaluation Plan contains the Clinical Development Plan

- The Clinical Development Plan shows the progression from exploratory investigations to confirmatory investigations
  - Exploratory investigations can include feasibility and pilot studies

  - Confirmatory investigations can include pivotal clinical investigations or a PMCF

Clinical Evaluation Report

- Article 61(2) requires documentation of any consultation with an expert panel

- Article 61(7) requires justification when the manufacturer does not perform clinical investigation for an implantable device or a Class III device where there is sufficient clinical evidence under the MDD or AIMD or for certain products (stales, sutures, *etc*.)

- The Annex XIV requires:
  - The results of the clinical evaluation
  - The clinical evidence used to obtain the results
  - The clinical evidence supports the assessment of conformity of the device

Risk Management (Plan, File, and Report)

Risk Management Plan

- Annex I(3)(a) requires a Risk Management Plan for every device
  - The EU-MDR doesn't specify the plans elements
- EN ISO 14971:2012 lists plan elements. ISO/DIS 14971 adds overall residual risk
  - Scope of the risk management plan
  - Assignment of responsibilities and authorities
  - Risk management review activities
  - Criteria for risk acceptability
  - *Acceptability criteria and evaluation of the overall residual risk*
  - Verification activities
  - Collection and review of production information
  - Collection and review of post-production information

Risk Management File

- Perform activities and documents them in a Risk Management File.
- Hazard Analysis
  - Identify hazards/sequences of events/hazardous situations/harms
  - Estimate the risk for each harm
- Evaluate the Risk Acceptability
  - Compare the estimated risk against the acceptability criteria
  - Eliminate or reduce the risk when it is not acceptable
- Risk Reduction
  - Implement risk control measures
  - Estimate the residual risk
  - Compare the estimate against the acceptability criteria
- Overall Residual Risk
  - Estimate the overall residual risk
  - Compare the estimate against the acceptability criteria
- Risk Management Report
- Collect and Review Production and Post-production Information
  - Update the previous work as necessary

Risk Management Activities

- Annex I(3) requires activities that fit into the Risk Management File
  - Identify and analyze the known and foreseeable hazards
  - Estimate and evaluate the risks associated with the intended use and reasonably foreseeable misuse
  - Eliminate or control the risks
  - Evaluate the information collected from the production phase
  - Evaluate the information collected from the post-production phase
  - Based on the evaluate amend the risk control measures as necessary

Risk Management Report

- EN ISO 14971:2012 and ISO/DIS 14971 both require a Risk Management Report

- The report documents the results of a review of the risk management process as applied to the device:
  - The Risk Management Plan has been implemented
  - The Overall Residual Risk is acceptable
  - Measures are in place to collect production information
  - Measures are in place to collect post-production information

Risk Management Outputs

- Definitions
  - *Residual Risk* means the risk remaining after risk control measures have been taken
  - Side-effect – Not defined

- The risk management process can provide three outputs useful to PMS
  - The residual risk
  - The overall residual risk
  - Side-effects
- The EU-MDR considers:
  - Side-effects
  - Expected side-effects
  - Undesirable side-effects
  - Expected undesirable side-effects
  - Unknown side-effects

Benefit-Risk Determination

Benefit-Risk Determination

- *Benefit-risk Determination* means the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer [Article 2(24)]

- *Reduce Risks As Far As Possible* means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio

- Article 61(1) Clinical Evaluation
  - Using clinical data to provide clinical evidence, evaluate the undesirable side-effects and the risk-benefit ratio for acceptability.
- Article 83(3)(a) PMS
  - Use PMS information to update the benefit-risk determination

Annex I and Annex II

- Annex I GS&PR
  - Section 1 requires that medical devices are safe and effective “provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient”
  - Section 8 requires, “All known and foreseeable risks, and any undesirable side-effects, shall be minimized and be acceptable when weighed against the evaluated benefits to the patient and/or user arising from the achieved performance of the device during normal conditions of use.”
- Annex II Technical Documentation
  - Section 5(a) requires that the technical documentation contain information on the benefit-risk analysis from Annex I Section 1 and Section 8.

Indicators and Thresholds

Indicators and Thresholds

- Annex III Technical Documentation On Post-market Surveillance
  - Section 1.1(b) says that the PMS Plan uses suitable indicators and threshold values in the continuous reassessment of the benefit-risk analysis

- Annex XIV Clinical Evaluation
  - Section 1(a) 5th indent says that the Clinical Evaluation Plan includes a list of parameters and their specifications to determine the acceptability of the benefit-risk ratio.

Conclusions

Conclusion

- Before putting the device on the market, perform a benefit/risk analysis to make a benefit/risk determination and use it to form a benefit/risk ratio.
- Identify the intended clinical benefits to patients
  - Annex XIV, Section 1(a) 4th indent requires them in the Clinical Evaluation Plan
- Identify both residual risk and side-effects
  - Annex XIV, Section 1(a) 5th indent requires them in the Clinical Evaluation Plan
- “Calculate” the Benefit-Risk Ratio
  - Annex XIV, Section 1(a) 6th indent requires that the Clinical Evaluation Plan contain a list and specification of the parameters to determine the acceptability of the benefit-risk ratio
- Identify Indicators and Threshold Values
  - Annex III, Section 1.1(b) requires them in the PMS Plan

Exercise B1

- Indicator and Threshold Analysis
- Use a hypothetical device and information from Clinical Evaluation and Risk Management to set indicators and thresholds to help make the Benefit-Risk Determination.

QUESTIONS