Workshop Introduction and the Overview of Post-market Activities

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Topics

- Introductions
- Identification of the Activities
- Role in the QMS
- Annex IX Documentation
- Notified Body Obligations
- Questions

Introductions

Speaker Biography

- Dan O'Leary
  - Dan O'Leary is President of Ombu Enterprises, LLC, an education, training, and consulting company focusing on Operational Excellence using analytical skills and a systems approach to operations management.
  - Dan has more than 30 years experience in quality, operations, and program management in regulated industries including aviation, defense, medical devices, and clinical labs.
  - He holds a Masters Degree in Mathematics; is an ASQ certified Biomedical Auditor, Quality Auditor, Quality Engineer, Reliability Engineer, and Six Sigma Black Belt; and is certified by APICS in Resource Management.

- Ombu Enterprises, LLC
  - Ombu works with small manufacturing companies, offering training and execution in Operational Excellence. Focusing on the analytic skills and systems approach of operations management, Ombu helps companies achieve efficient, effective process and regulatory compliance.

Participant Introduction

- Your Name
- Your company
- Your job title (what do you really do?)
- What kind of devices does your division or company manufacture?
- Do you presently sell your device in the EU under the MDD, IVDD, or the AIMD

NOTICE
You may have a competitor in the room!
Be careful what you say

Ground Rules

- Our approach is casual
- Silence your cell phones during the class
- Ask lots of questions
- Bring examples from your experience
- Participate
- Have fun!

Role of the QMS

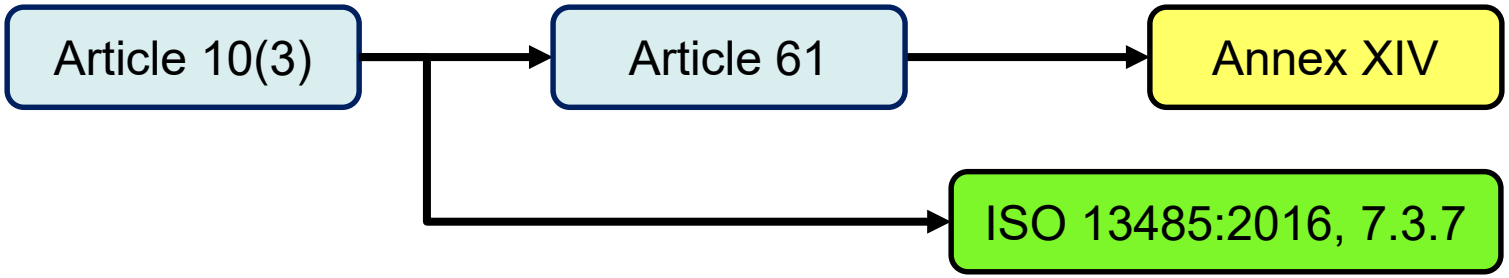
The QMS

- The QMS contains all elements of the post-market activities.
- They start in Article 10, Obligations of the Manufacturer
- The Article splits the requirements into two linked pieces
  - One piece is the obligation of the manufacturer to implement the element
  - The other piece is to include it in the QMS

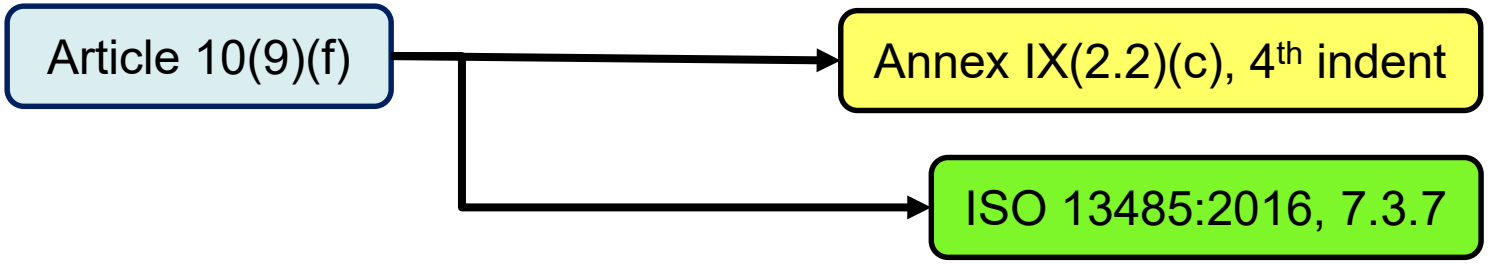
CEN/TR 17223:2018

- CEN/TR 17223:2018 follows each path through the MDR.
- The end point of each path ISO 13485:2016
- The paths are either:
  - The implementation path
  - The QMS application path

Example – Clinical Evaluation



Clinical Evaluation as Part of the QMS



Identification of the Activities

PMS as A Матрешка Doll

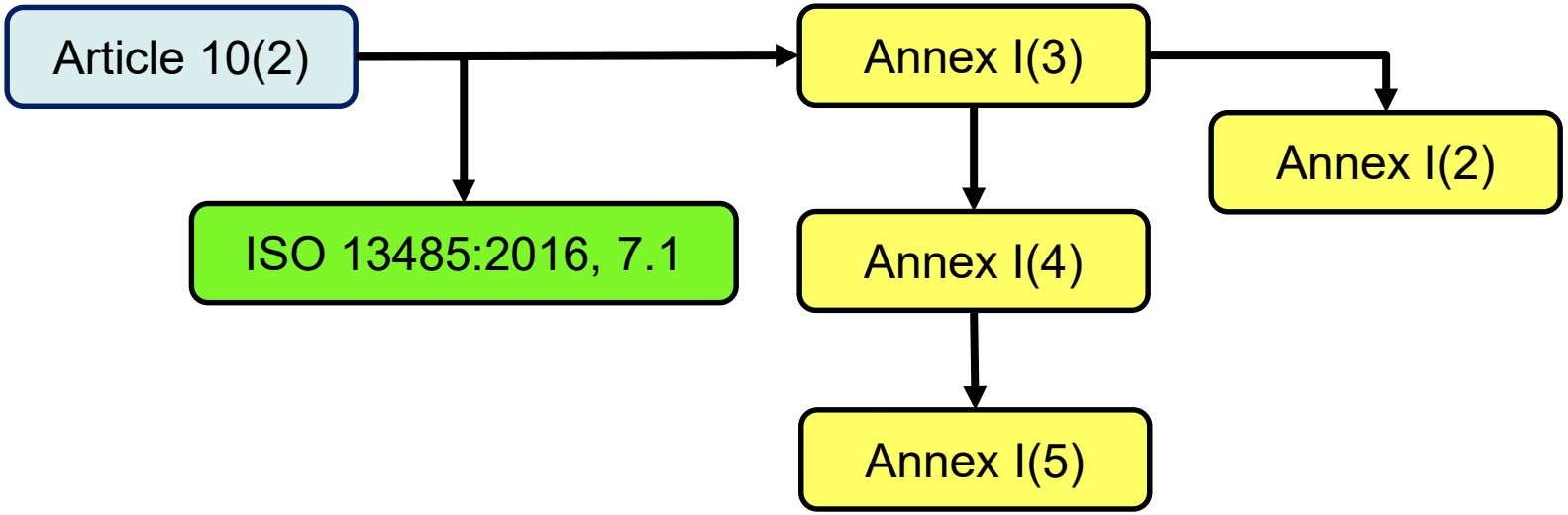
The PMS System:

Plans inside plans

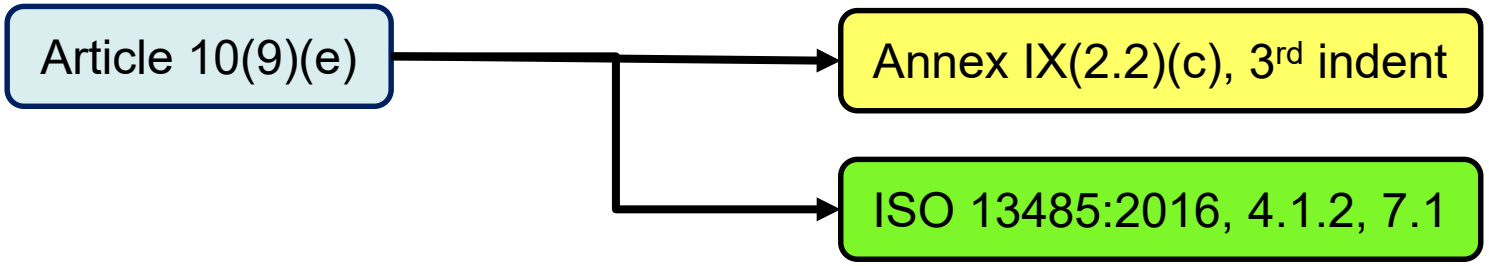
Reports inside reports

Risk Management

RMS



RMS as Part of the QMS



RMS – Annex I(3)

- In carrying out risk management manufacturers shall:

  (a) establish and document a risk management plan for each device

  (b) identify and analyze the known and foreseeable hazards associated with each device

  (c) estimate and evaluate the risks associated with, and occurring during, the intended use and during reasonably foreseeable misuse

  (d) eliminate or control the risks referred to in point (c) in accordance with the requirements of Section 4

  (e) evaluate the impact of information from the production phase and, in particular, from the post-market surveillance system, on hazards and the frequency of occurrence thereof, on estimates of their associated risks, as well as on the overall risk, benefit-risk ratio and risk acceptability

  (f) based on the evaluation of the impact of the information referred to in point (e), if necessary amend control measures in line with the requirements of Section 4.

RMS – Annex I(4)

- Use the following priority order for selecting risk control measures:
  (a) eliminate or reduce risks as far as possible through safe design and manufacture

  (b) where appropriate, take adequate protection measures, including alarms if necessary, in relation to risks that cannot be eliminated

  (c) provide information for safety (warnings/precautions/contra-indications) and, where appropriate, training to users.

- Inform users of any residual risks.

RMS – Annex I(5)

- In eliminating or reducing risks related to use error:

  (a) reduce as far as possible the risks related to the ergonomic features of the device and the environment in which the device is intended to be used (design for patient safety)

  (b) give consideration to the technical knowledge, experience, education, training, and use environment, where applicable, and the medical and physical conditions of intended users (design for lay, professional, disabled, or other users)

Benefit-Risk Determination (BRD)

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 [Art. 2(24)]

- *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(s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health [Art. 2(53)]

- *Risk* means the combination of the probability of occurrence of harm and the severity of that harm [Art. 2(23)]

Benefit-Risk Determination

- Clinical Evaluation helps evaluate the "acceptability of the benefit-risk ratio" [Art. 61(1)]
- Post-market Surveillance helps "update the benefit-risk determination" [Art. 83(3a)]
- The Periodic Safety Update Report, PSUR, sets out "the conclusions of the benefit-risk determination" [Art. 86(1a)]
- To *reduce risks as far as possible* means the reduction of risks as far as possible without adversely affecting the benefit-risk ratio [Anx. I(2)]

Benefit-Risk Determination

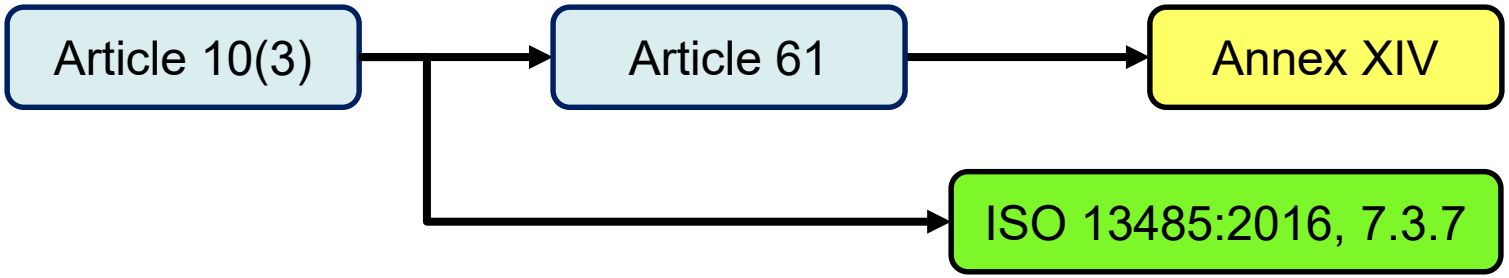
- Evaluate the impact of information … from the post-market surveillance system on the overall risk, benefit-risk ratio, and risk acceptability [Anx. I(3e)]

- The Technical Documentation contains information on the benefit-risk analysis [Anx. II(5a)]

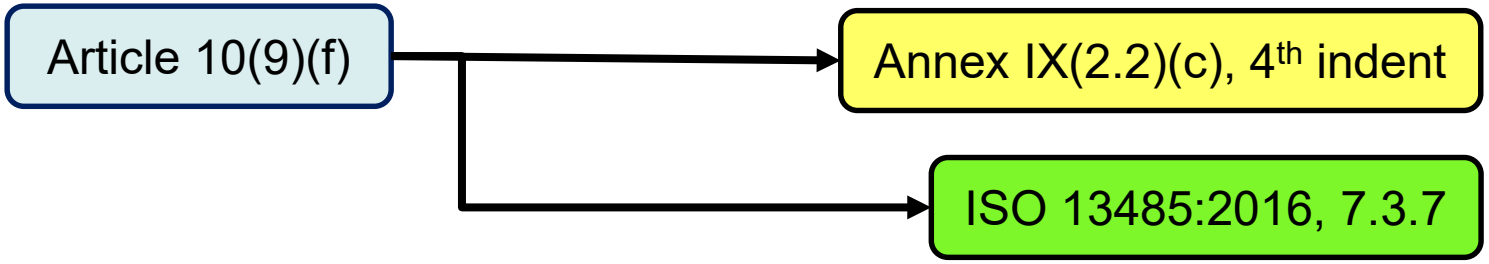
- The Post-market Surveillance Plan covers suitable indicators and threshold values used in the continuous reassessment of the benefit- risk analysis [Anx. III(1.1b)]

Clinical Evaluation (CE)

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)]

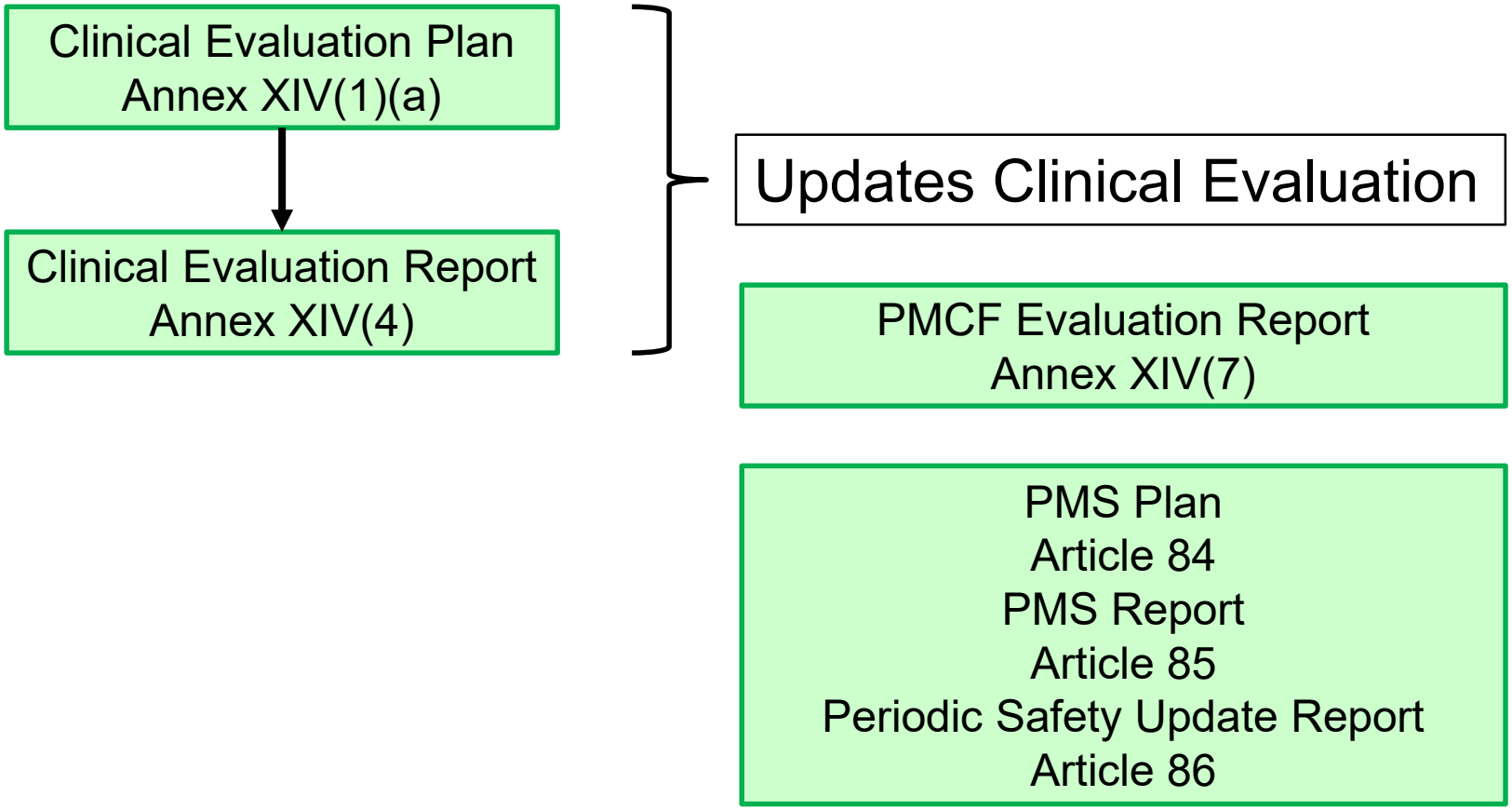
Definitions

- *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

Article 61(1)

- Use clinical data providing sufficient clinical evidence to:
  - Confirm conformity with the Annex I requirements
  - Evaluate undesirable side effects
  - Evaluate the acceptability of the benefit-risk ratio

- Plan, conduct, and document a clinical evaluation in accordance with Article 61 and Annex XIV, Part A.

Article 61(3)

- Clinical evaluation follows a defined and methodologically sound procedure based on:

  (a) A critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics, and intended purpose of the device, where the following conditions are satisfied

  — it is demonstrated that the device subject to clinical evaluation for the intended purpose is equivalent to the device to which the data relate (see Annex XIV(3))

  — the data adequately demonstrate compliance with the relevant general safety and performance requirements

  (b) A critical evaluation of the results of all available clinical investigations

  (c) A consideration of currently available alternative treatment options for that purpose, if any

Article 61(11)

- Update the clinical evaluation and its documentation throughout the life-cycle from:
  - The results of the PMCF plan in Annex XIV, Part B
  - The results PMS plan in Article 84

- For class III devices and implantable devices annually update the:
  - The PMCF evaluation report
  - And the Summary of Safety and Clinical Performance, SSCP (see Article 32)

Article 61(12)

- Document the clinical evaluation, its results, and the clinical evidence in a Clinical Evaluation Report (see Annex XIV(4))

- The Clinical Evaluation Report is part of the Annex II technical documentation

Annex XIV(1)(a)

- The **Clinical Evaluation Plan** includes:
  - Identification of the Annex I requirements that need clinical evaluation
  - The intended purpose of the device
  - The intended target groups with indications and contra-indications
  - Intended clinical benefits and clinical outcome
  - The methods used including determination in residual risk and side-effects
  - The method to determine the acceptability of the benefit-risk ratio
  - How to address benefit-risk issues related to certain components
  - A clinical development plan

Annex XIV(4)

- The **Clinical Evaluation Report**:
  - Support the assessment of the conformity of the device
  - Demonstrates conformity with the Annex I General Safety and Performance Requirements
  - Is part of the technical documentation for the device
  - Includes both favorable and unfavorable data considered in the clinical evaluation

Equivalence – Annex XIV(3)

- A clinical evaluation **may** be based on clinical data relating to a device for which equivalence to the device in question can be demonstrated.

- Equivalence takes into account technical, biological, and clinical characteristics
  - The section includes a discussion of each one

- There should be no clinically significant difference in the safety and clinical performance of the equivalent device, based on proper scientific justification

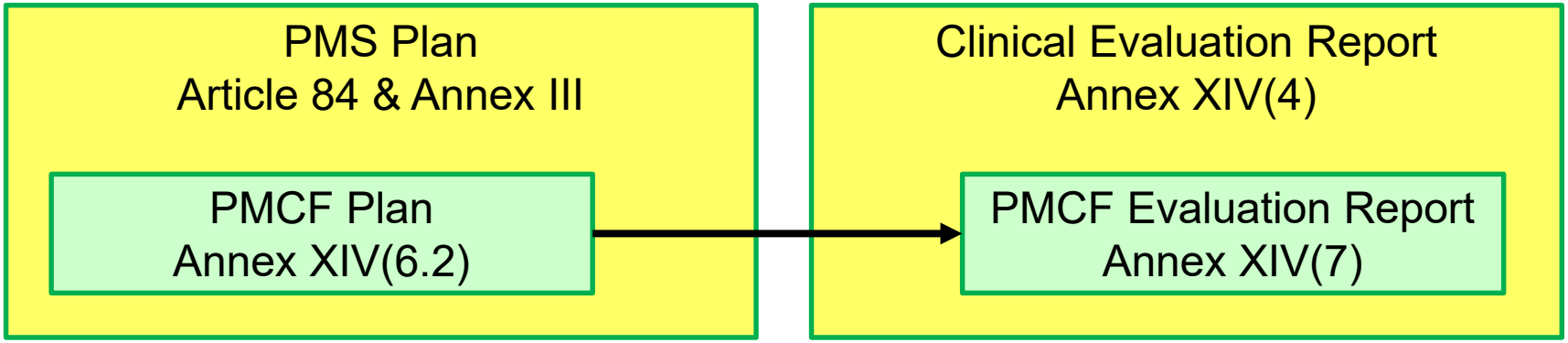
- The manufacturer clearly demonstrates access to the data to justify the claim of equivalence

Equivalence – Article 61(5)

- Implantable and Class III devices require clinical investigation, but there are expectations
  - One question is the role of an equivalent device from another manufacturer

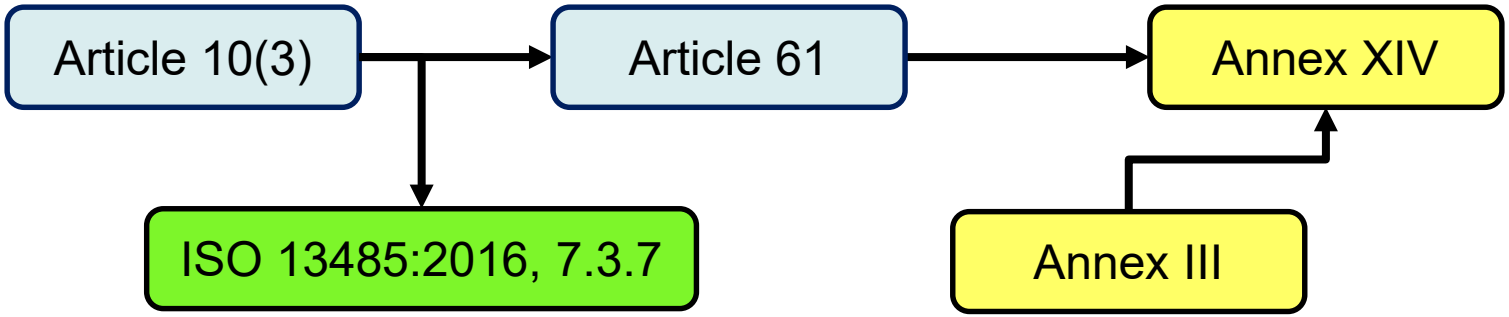
- The other device may be use as part of an exception to a clinical investigation when:
  - The two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis
  - The original clinical evaluation was performed in compliance with the EU-MDR
  - The manufacturer of the second device provides clear evidence to the Notified Body

Containment

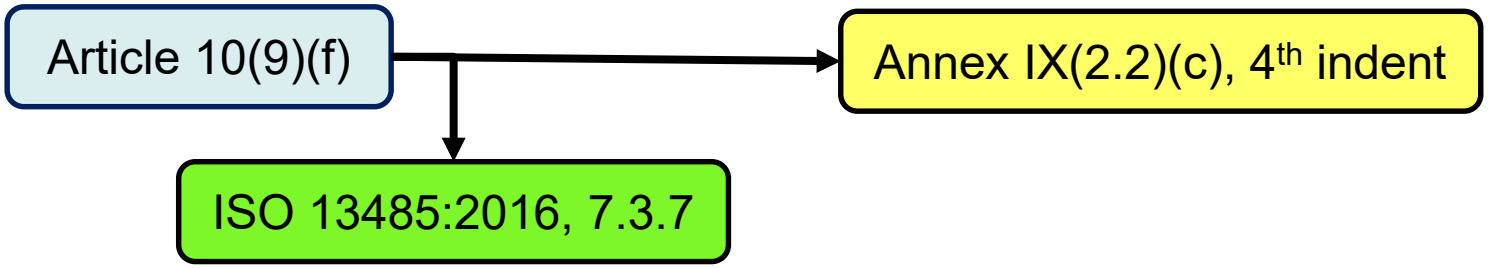


Post-Market Clinical Follow-up (PMCF)

PMCF



PMCF as Part of the QMS



Annex XIV(6.2)

- The **Post-Market Clinical Follow-up Plan** includes:
  - General methods and procedures
  - Specific methods and procedures
  - A rationale for the methods and procedures
  - A reference to the relevant parts of the Clinical Evaluation Report
  - A reference to the relevant parts of risk management
  - The specific objectives
  - An evaluation of the clinical data relating to equivalent or similar devices
  - Reference to any relevant CS, harmonized standard, and guidance on PMCF
  - A detailed and justified time schedule for PMCF activities

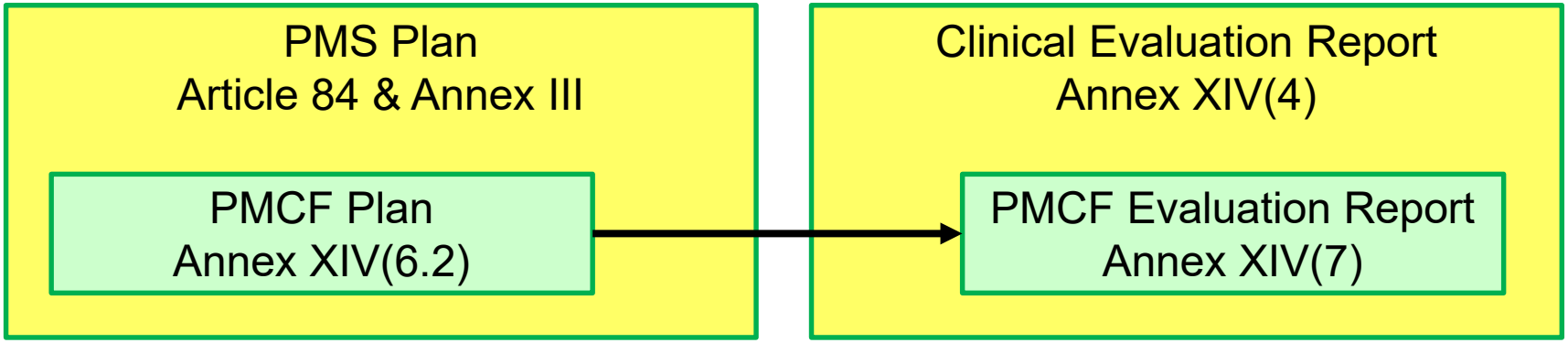
Annex III(1.1)(a)

- The post-market surveillance plan covers:
  - The PMCF plan from Annex XIV, Part B
  - A justification as to why a PMCF is not applicable

Annex XIV(7)

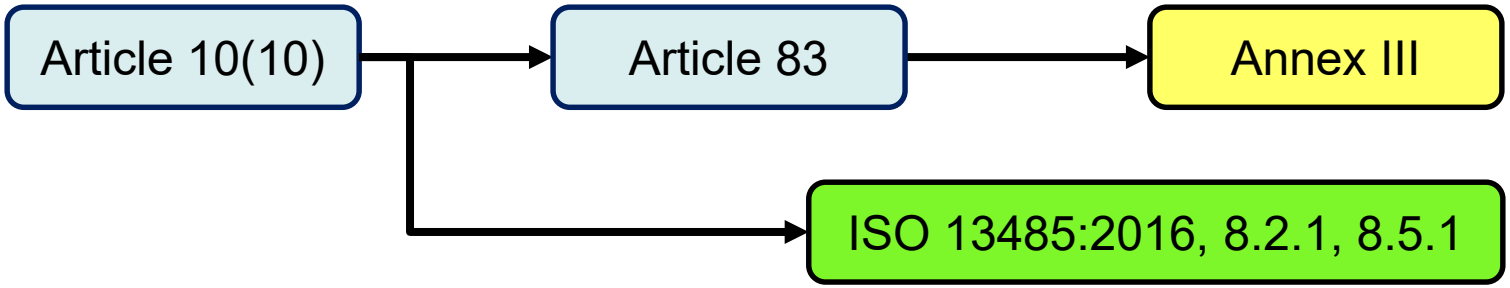
- Analyze the findings of the PMCF
- Document the results in a PMCF Evaluation Report
- The report becomes part of the Clinical Evaluation Report
- The report becomes part of the technical documentation

Containment

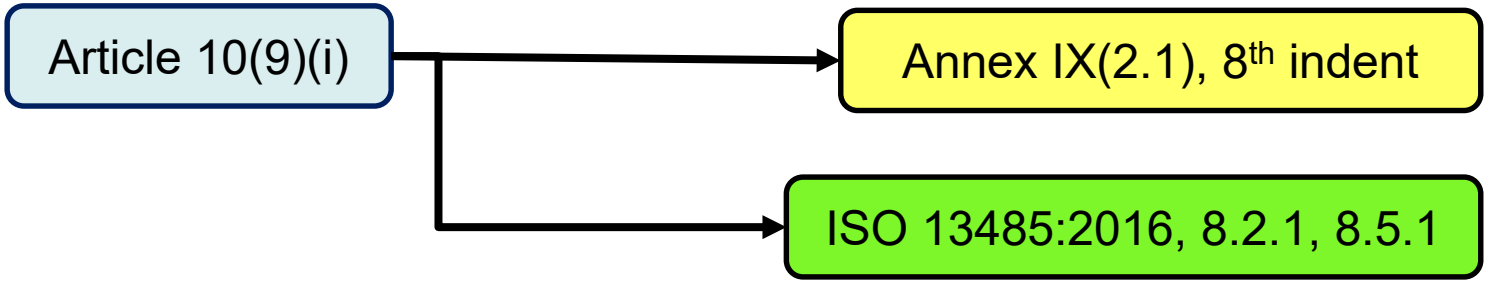


Post-Market Surveillance

PMS



Clinical Evaluation as Part of the QMS



Definitions

- *Post-market Surveillance* means all activities carried out by manufacturers in cooperation with other economic operators to institute and keep up to date a systematic procedure to proactively collect and review experience gained from devices they place on the market, make available on the market or put into service for the purpose of identifying any need to immediately apply any necessary corrective or preventive actions [Art. 2(60)]

- *Market Surveillance* means the activities carried out and measures taken by competent authorities to check and ensure that devices comply with the requirements set out in the relevant Union harmonization legislation and do not endanger health, safety or any other aspect of public interest protection [Art. 2(61)]

Article 83 & 84

- For each device, plan, establish, document, implement, maintain, and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device.
- The PMS system is an integral part of the manufacturer's quality management system referred to in Article 10(9).
- The post-market surveillance system referred to in Article 83 is based on a post-market surveillance plan (see Annex III(1.1)).
- The post-market surveillance plan is part of the technical documentation specified in Annex II.

Annex III(1.1)(b)

- The PMS Plan covers (partial list):
  - A proactive and systematic process to collect information
  - Effective and appropriate methods and processes to assess the collected data
  - Suitable indicators and threshold values for reassessment of the benefit-risk analysis and risk management
  - Effective and appropriate methods and tools to investigate complaints and analyze market-related experience collected in the field
  - Methods and protocols to manage the events subject to trend report, including methods and protocols to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period
  - The PMCF plan (see Annex XIV, Part B) or a justification as to why a PMCF is not applicable

Article 85

- Manufacturers of Class I devices prepare a post-market surveillance report summarizing the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 84 together with a rationale and description of any preventive and corrective actions taken.

- The report is updated when necessary and made available to the competent authority upon request

Article 86

- Manufacturers of Class IIa, Class IIb and Class III devices prepare a periodic safety update report ('PSUR') for each device and where relevant for each category or group of devices.

- Manufacturers of Class IIa devices update the PSUR at least every two years.
- Manufacturers of Class IIb and Class III devices update the PSUR at least annually.

- For Class III devices or implantable devices, manufacturers submit PSURs electronically to the Notified Body. The Notified Body reviews the PSUR and sends it to the Competent Authority.

- For other devices, manufacturers make PSURs available to the Notified Body and, upon request, to Competent Authorities.

Summary of Safety and Clinical Performance (SSCP)

Article 32(1)

- For implantable devices and for Class III devices, the manufacturer prepares a Summary Of Safety And Clinical Performance
  - It is written to be clear to the intended user and, if relevant, to the patient and is made available to the public via Eudamed

- The draft of the Summary Of Safety And Clinical Performance is part of the shall be part of the documentation submitted to the Notified Body as part of conformity assessment.

- The Notified Body validates the summary and uploads it to Eudamed.

- The manufacturer mentions on the label or instructions for use where the summary is available.

Article 32(2)

- The SSCP includes:
  - Identification of the device (including the basic UDI-DI) and the manufacturer (including the SRN)
  - The intended purpose of the device and any indications, contraindications, and target populations
  - A description of the device including previous generations, variants, accessories, or other devices used in combination
  - Possible diagnostic or therapeutic alternatives
  - Reference to any harmonized standards and CS applied
  - A summary of the clinical evaluation and relevant information on PMCF
  - Suggested profile and training for users
  - Information on any residual risks and any undesirable effects, warnings, and precautions

Vigilance & Trend Analysis

Definitions

- *Incident* means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect [Art. 2(64)]

- *Serious Incident* means any incident that directly or indirectly led, might have led or might lead to any of the following:

  (a) the death of a patient, user or other person

  (b) the temporary or permanent serious deterioration of a patient's, user's, or other person's state of health

  (c) a serious public health threat [Art. 2(65)]

- *Field Safety Corrective Action* means corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market [Art. 2(68)]

Article 87(1)

- Manufacturers report to the relevant competent authorities:

  (a) any serious incident, except expected side-effects which are clearly documented in the product information and quantified in the technical documentation and are subject to trend reporting pursuant to Article 88

  (b) any field safety corrective action including any field safety corrective action undertaken in a third country in relation to a device which is also legally made available on the Union market, if the reason for the field safety corrective action is not limited to the device made available in the third country

Reporting Times

- Report serious incidents immediately, but not later than 15 days after becoming aware of the incident
- In the event of a serious public health threat report immediately, but not later than 2 days after becoming aware of the incident
- In the event of death or an unanticipated serious deterioration in a person's state of health the report shall be provided immediately, but not later than 10 days after becoming aware of the incident

Article 88 Trend Reporting

- Report any statistically significant increase in the frequency or severity of:
  - Incidents that are not serious incidents
  - Incidents that are expected undesirable side-effects

- Establish the significant increase in comparison to the foreseeable frequency or severity of such incidents in respect of the device, device category, or group of devices during a specified period

- The PMS plan specifies:
  - Management of the incidents
  - The methodology to determine any statistically significant increase in the frequency or severity of the incidents
  - The observation period

Annex IX Documentation

Annex IX

- Annex IX is one of the conformity assessment paths. It applies to Class IIa, Class IIb, and Class III devices.
- Annex IX includes a requirement to submit QMS documentation to the NB and to maintain it.
- The NB will review the initial documentation, cover it in the QMS assessment, in the initial audit, and in surveillance audits.
- Paths in CEN/TR 17223:2018 related to Article 10, section 9 usually lead to Annex IX requirements.

Annex IX Structure

- Annex IX has the following sections. Each has some items relevant to post-market.

- 2 Quality management system assessment
- 2.1 Submit an application for assessment
- 2.2 Implement the QMS to comply with the regulation
- 2.3 Audit
- 2.4 Inform the NB of plans of substantial changes to the QMS
- 3 Surveillance assessment for Class IIa, Class IIb, and Class III devices
- 4 Technical documentation assessment for Class III and Class IIb devices
- 5 Specific additional procedures
- 5.1 Assessment procedure for certain class III and class IIb devices

Notified Body Obligations

Annex IX

- Section 3.3
- Notified bodies shall periodically, at least once every 12 months, carry out appropriate audits and assessments to make sure that the manufacturer in question applies the approved quality management system and the post-market surveillance plan.

Annex VII

- 4.5.2. Quality management system auditing
- Develop a sampling plan for Class IIa and Class IIb to assess the Annex II and Annex III technical documentation.
  - All devices covered by the certificate are sampled over the certificates' validity period.
- Based on the technical documentation review the manufacturer’s processes and subsystems for:
  - design and development
  - production and process controls
  - product documentation
  - purchasing controls including verification of purchased devices
  - corrective and preventive actions
  - post-market surveillance
  - PMCF

QUESTIONS