# IVDR Technical Documentation

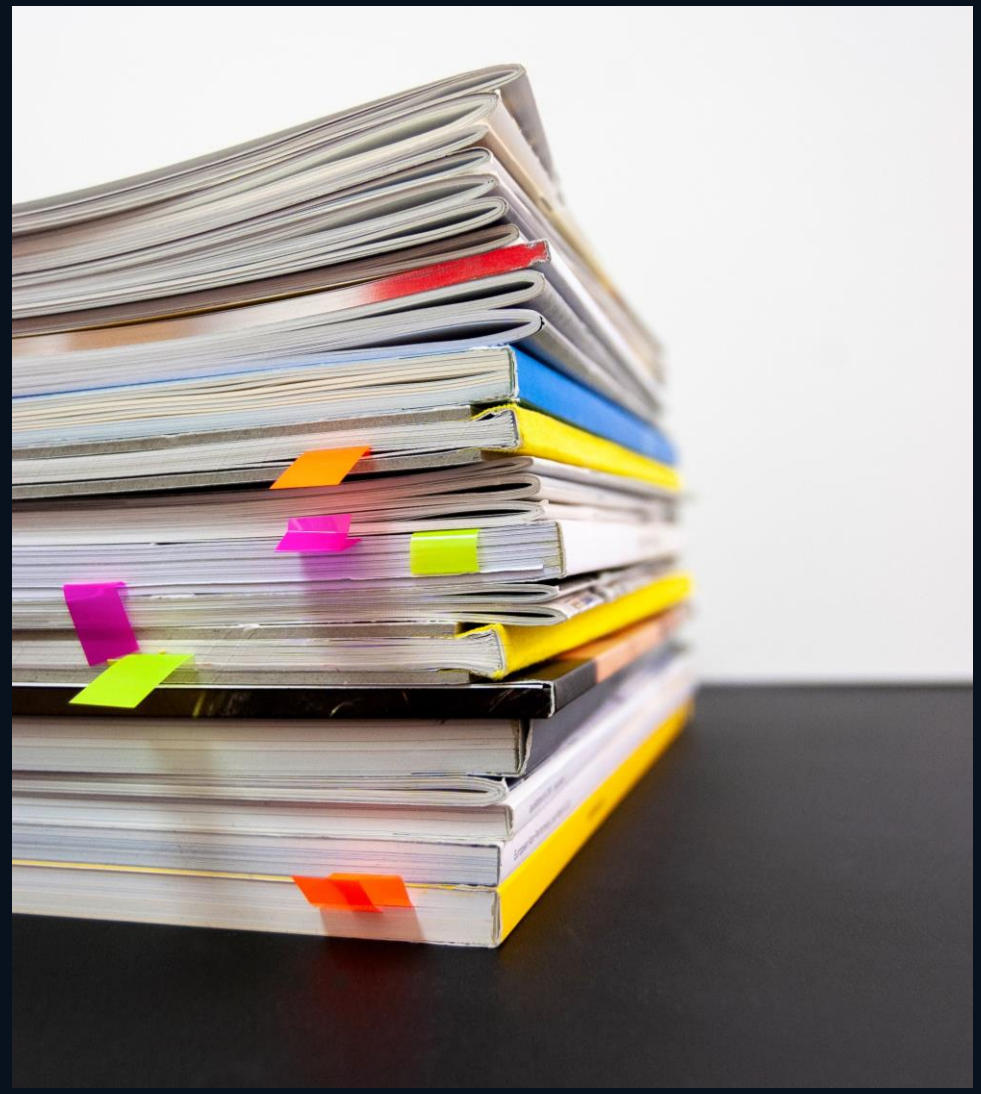
Notified Body Expectations and Lessons Learned

Stefan Burde



From AMDM Annual Meeting April 2015

# What is IVDR Technical Documentation?



# What is not IVDR Technical Documentation?



## IVDD Technical file

DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 27 October 1998

on *in vitro* diagnostic medical devices

**RICHTLINIE 98/79/EG DES EUROPÄISCHEN PARLAMENTS UND DES RATES**

**vom 27. Oktober 1998**

**über In-vitro-Diagnostika**

DIRECTIVE 98/79/CE DU PARLEMENT EUROPÉEN ET DU CONSEIL

du 27 octobre 1998

relative aux dispositifs médicaux de diagnostic in vitro

# What is not IVDR Technical Documentation?



## IVDD Technical file

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## IVDD Technical file


## FDA 510(k) Submission

# What is not IVDR Technical Documentation?



## IVDD Technical file


## FDA 510(k) Submission

# So how do we know what it is?

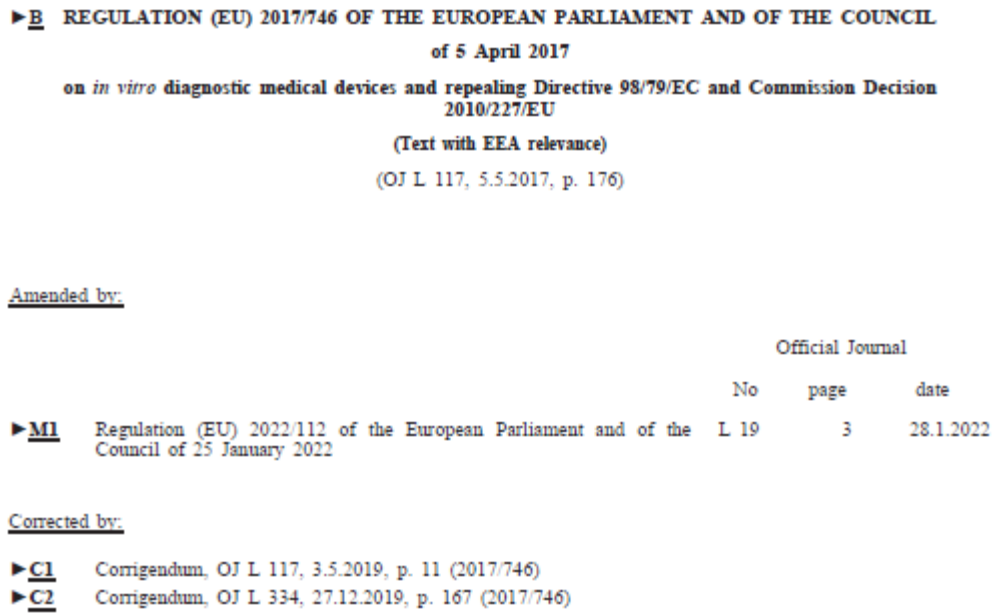


IVDR (EU) 2017/746

Annex II Technical Documentation

Annex III Technical Documentation on Post-market Surveillance

Annex XIII Performance Evaluation, Performance Studies and Post-market Performance Follow-up



►B REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 5 April 2017

on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

(Text with EEA relevance)

(OJ L 117, 5.5.2017, p. 176)

Amended by:

| | | Official Journal No | page | date |
|---|---|---|---|---|
| ►M1 | Regulation (EU) 2022/112 of the European Parliament and of the Council of 25 January 2022 | L 19 | 3 | 28.1.2022 |

Corrected by:

►C1 Corrigendum, OJ L 117, 3.5.2019, p. 11 (2017/746)
►C2 Corrigendum, OJ L 334, 27.12.2019, p. 167 (2017/746)

Yeah, Yeah, we know.

But what do Notified Bodies expect?

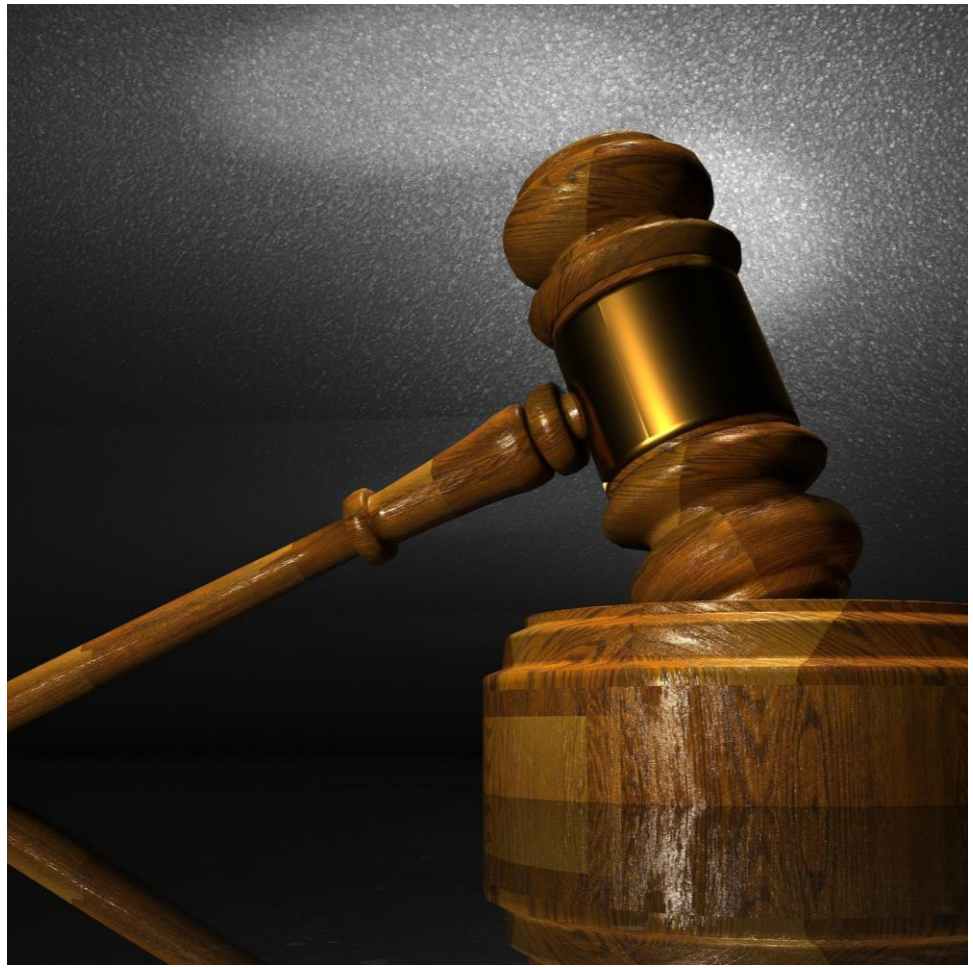
# File Organisation



Annex II First Paragraph:

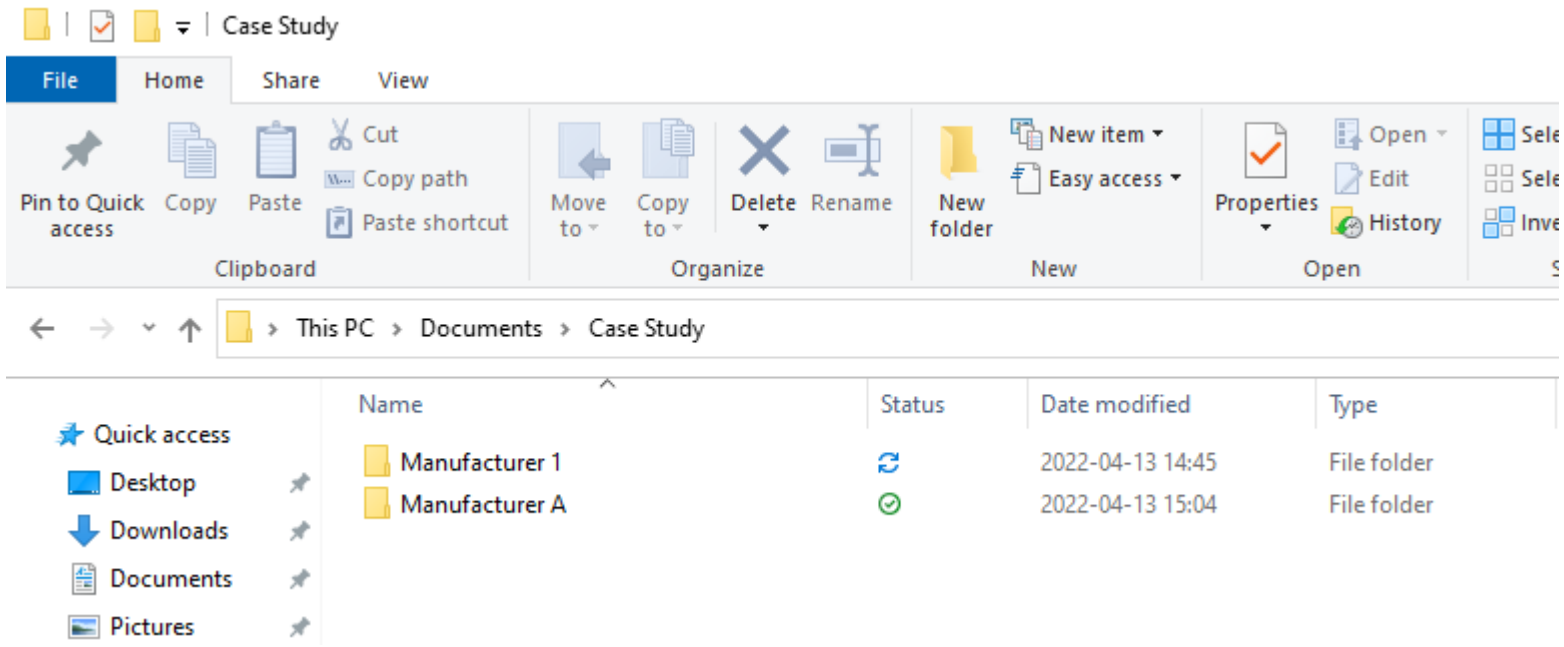
**The technical documentation and, if applicable, the summary thereof to be drawn up by the manufacturer shall be presented in a clear, organised, readily searchable and unambiguous manner and shall include in particular the elements listed in this Annex.**

Note: BSI does not require a prescribed document structure, but we do evaluate technical documentation against the above requirement.



# Case Study

## Searching for PMPF planning



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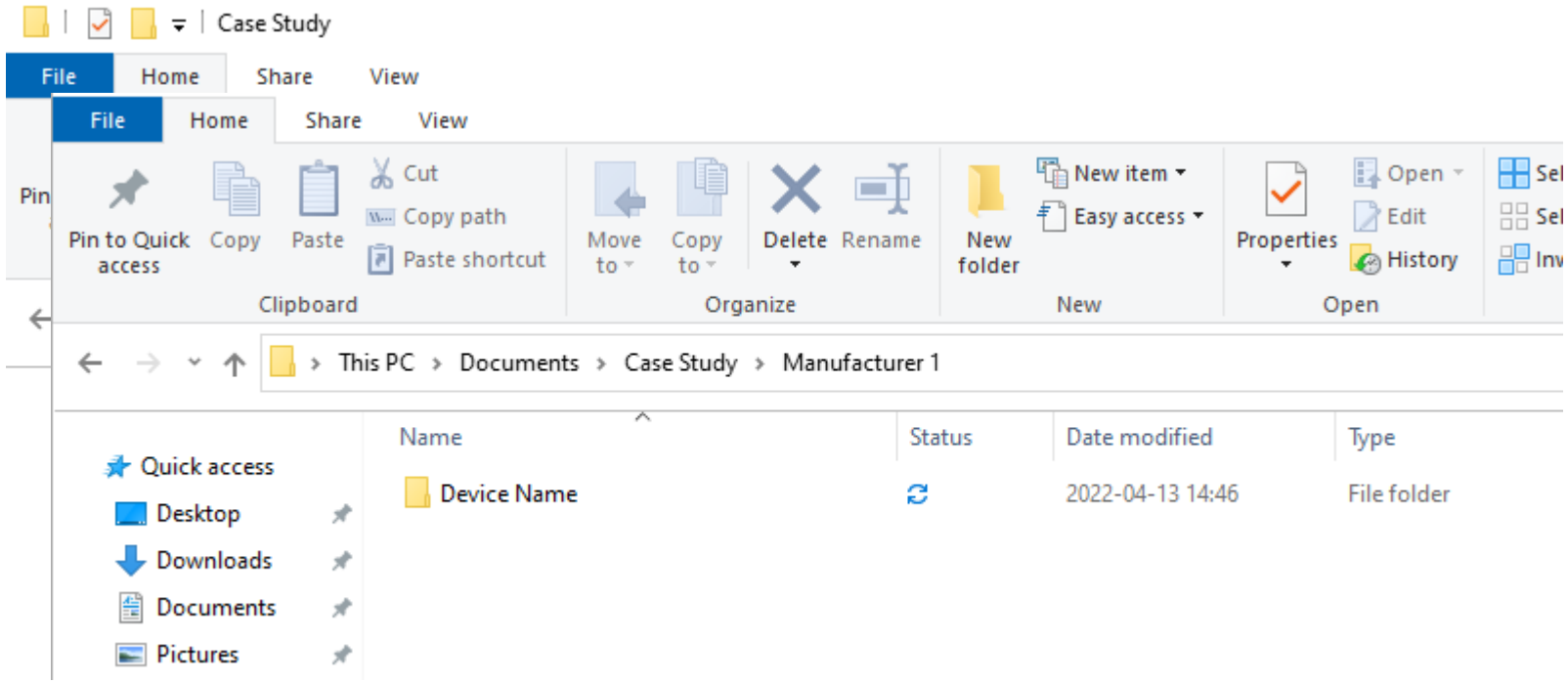

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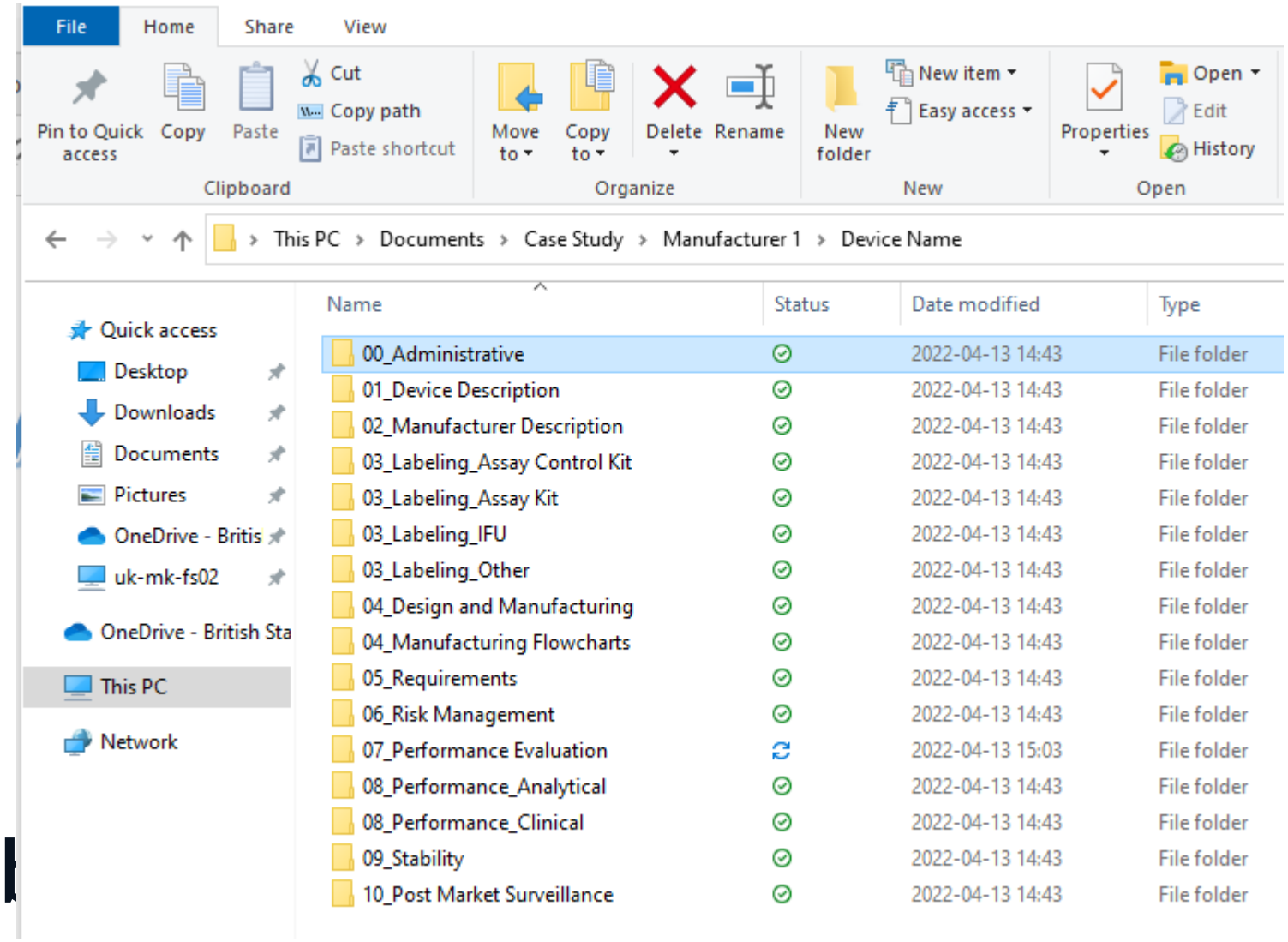

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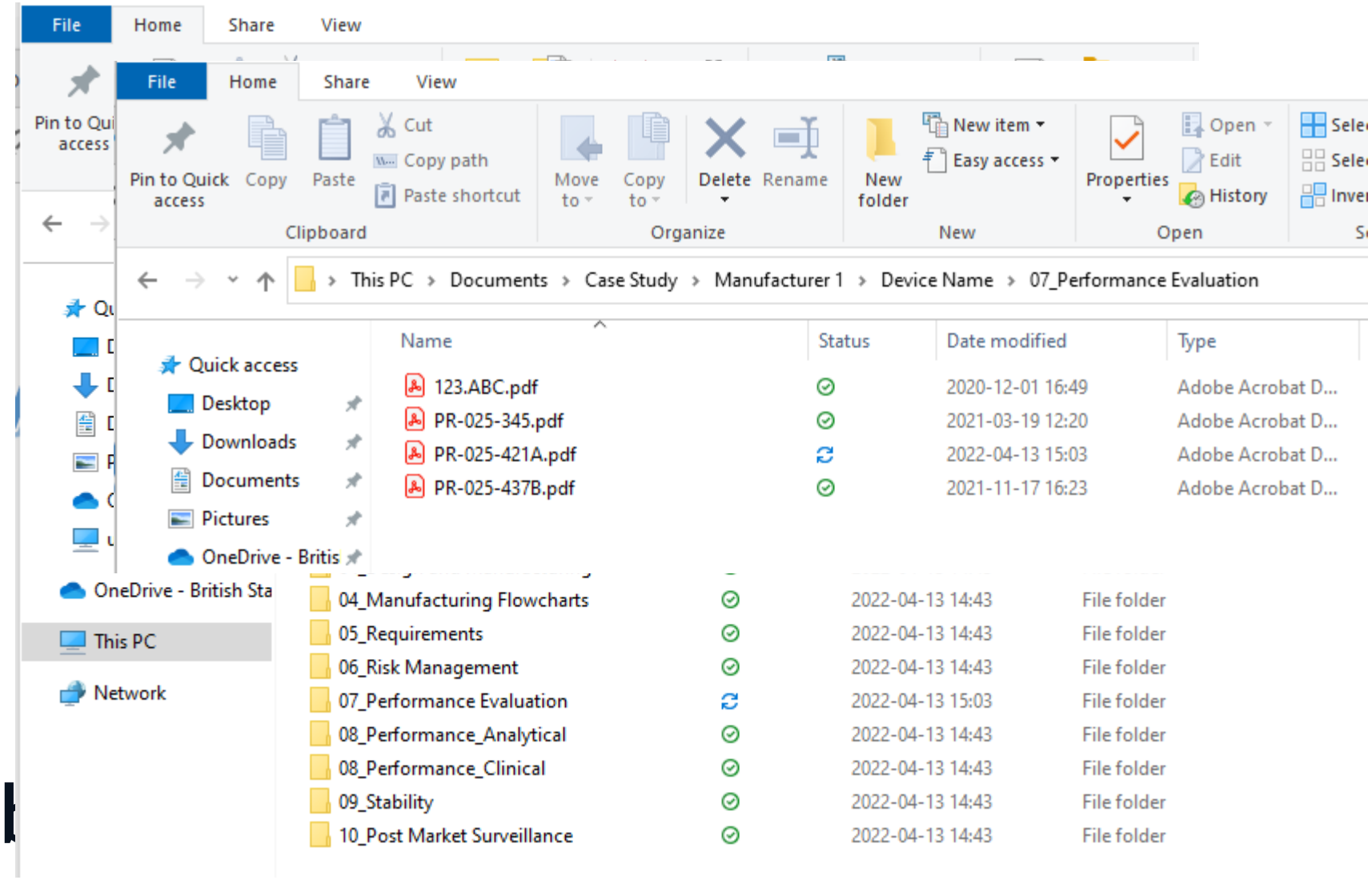

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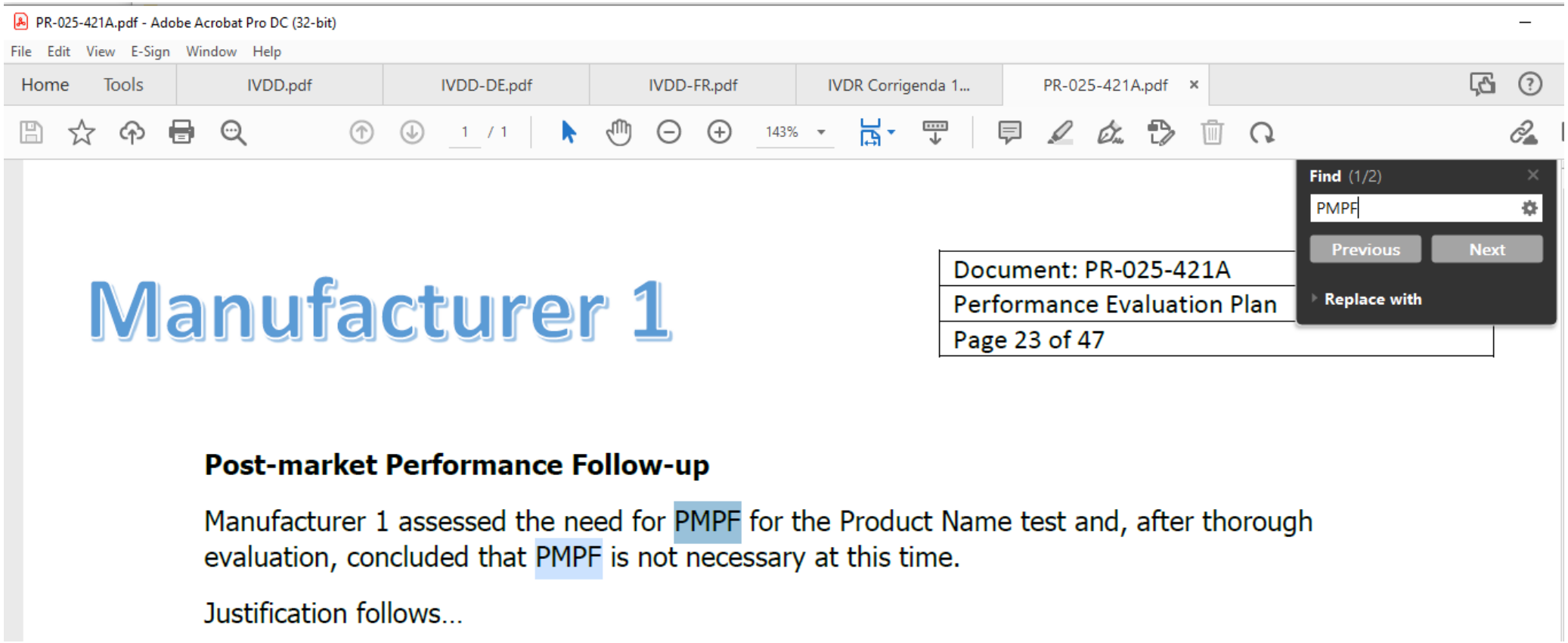

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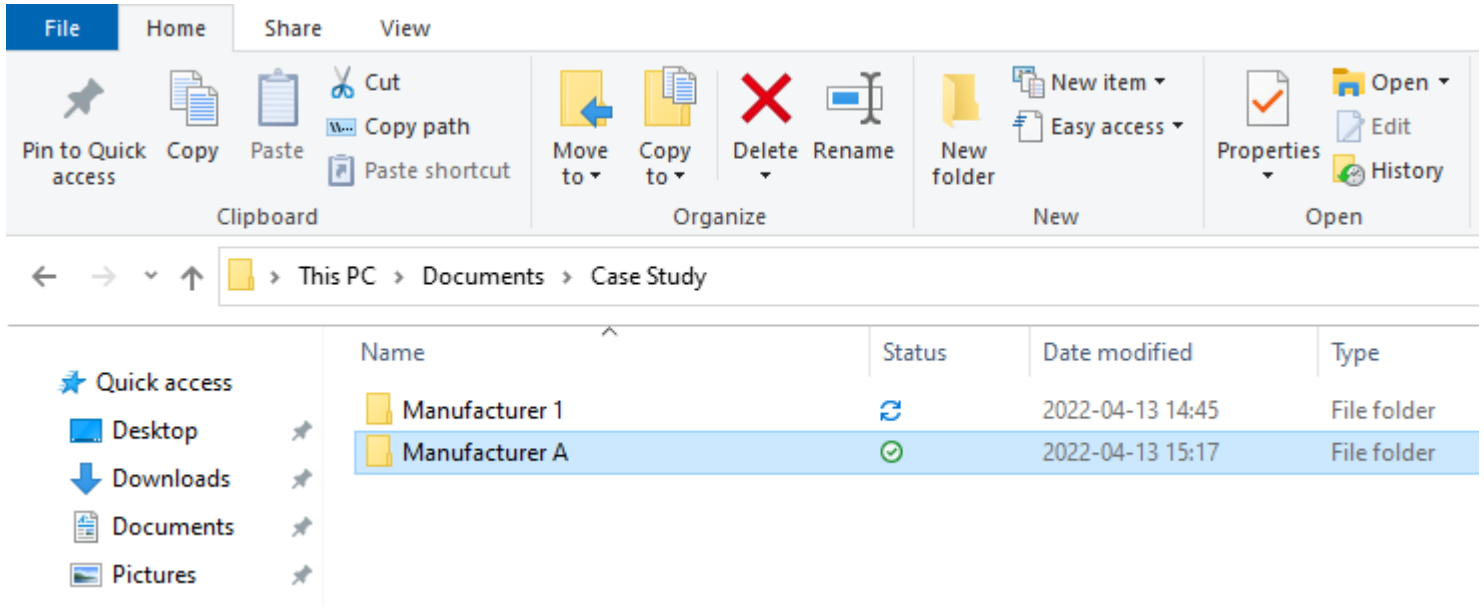

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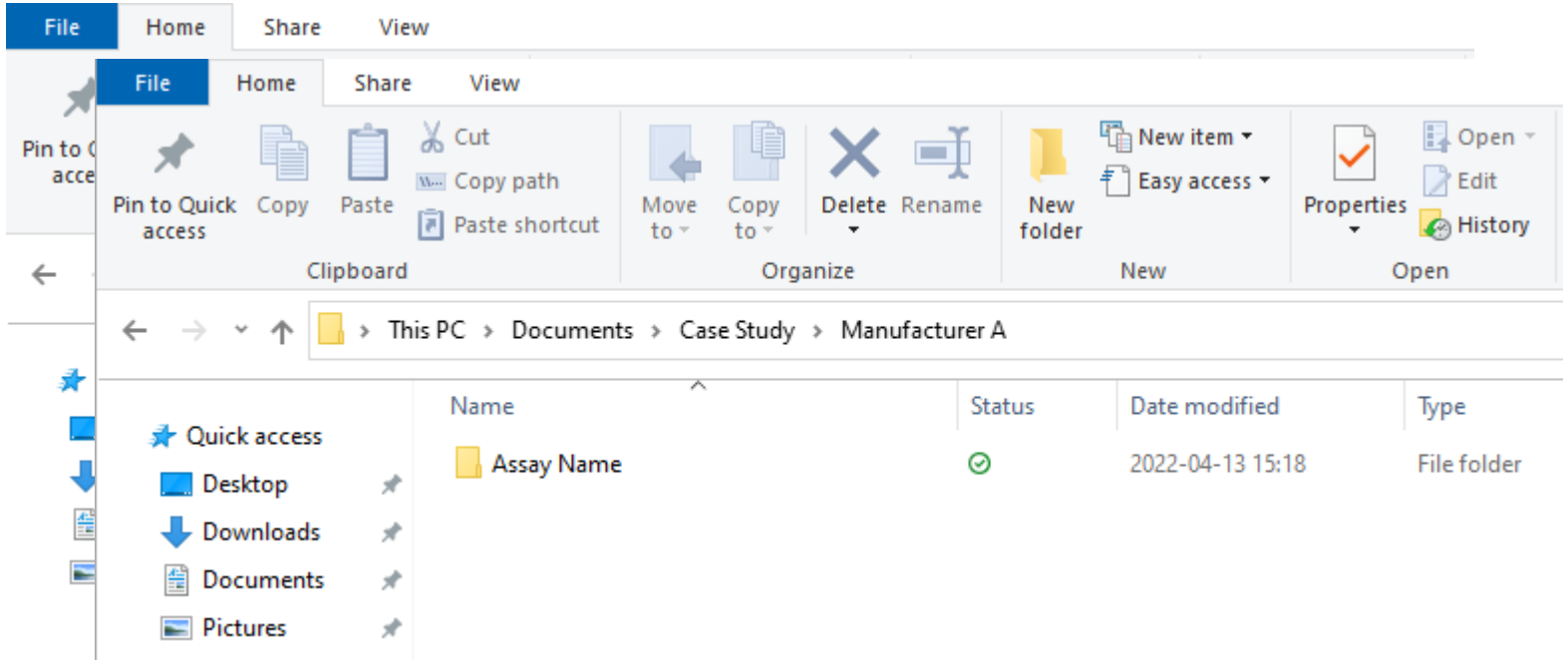

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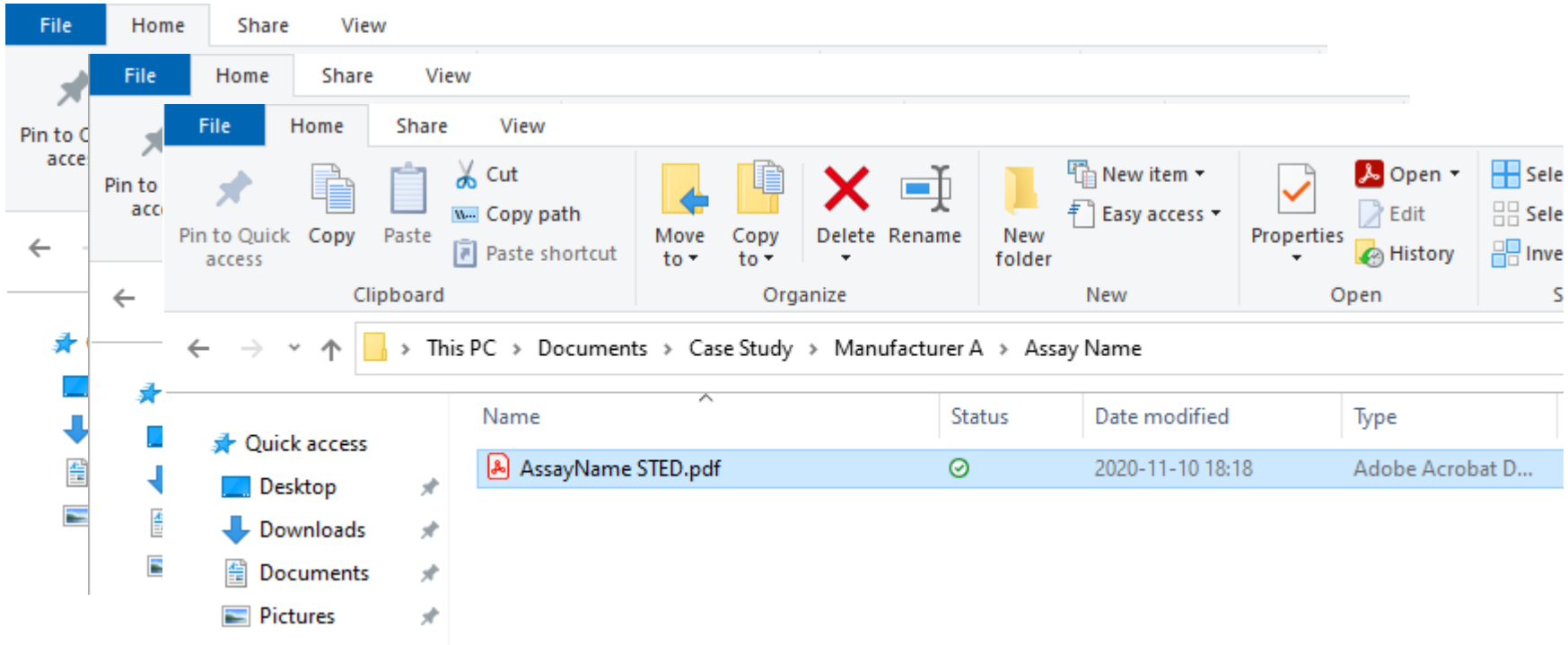

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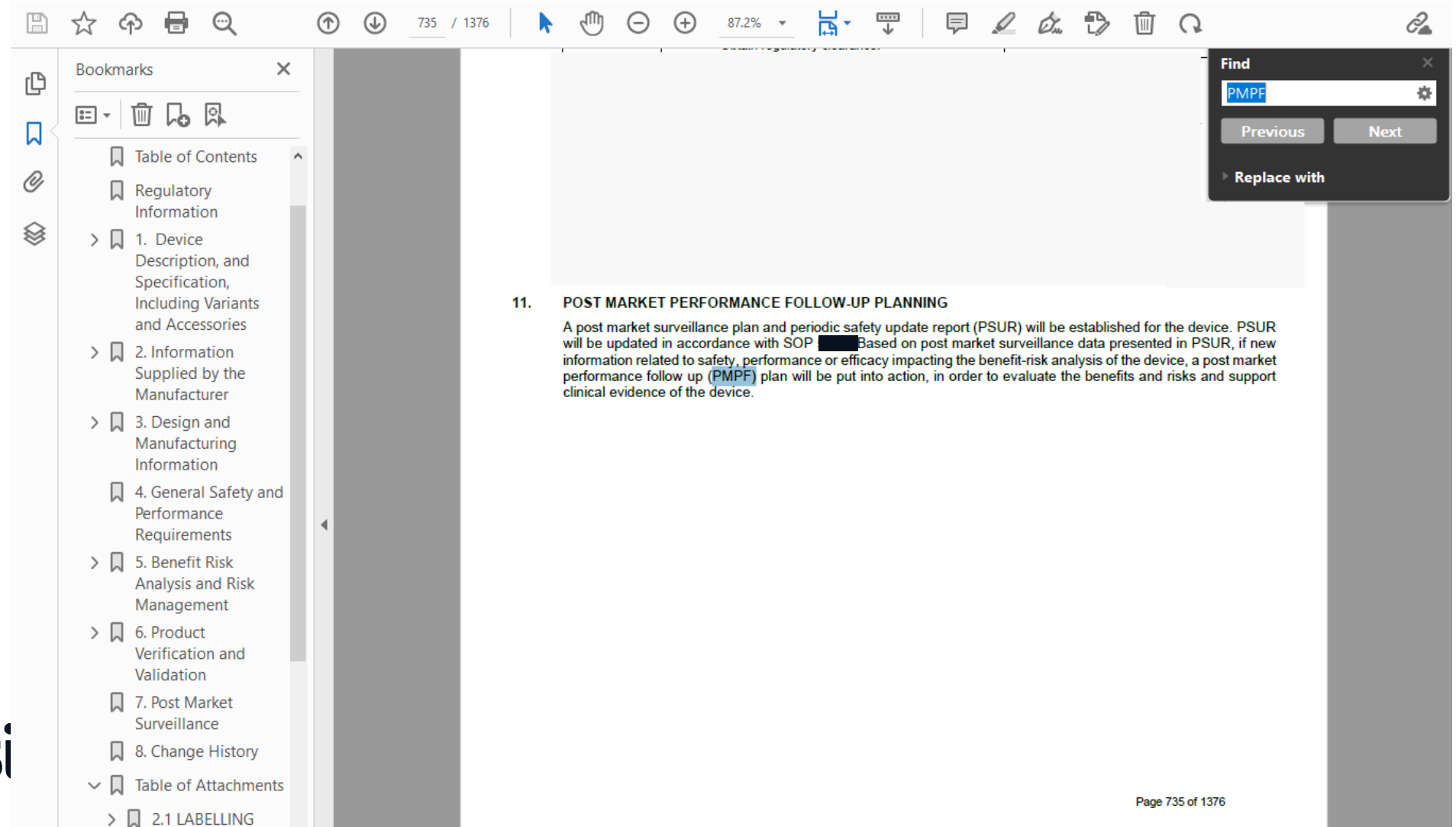
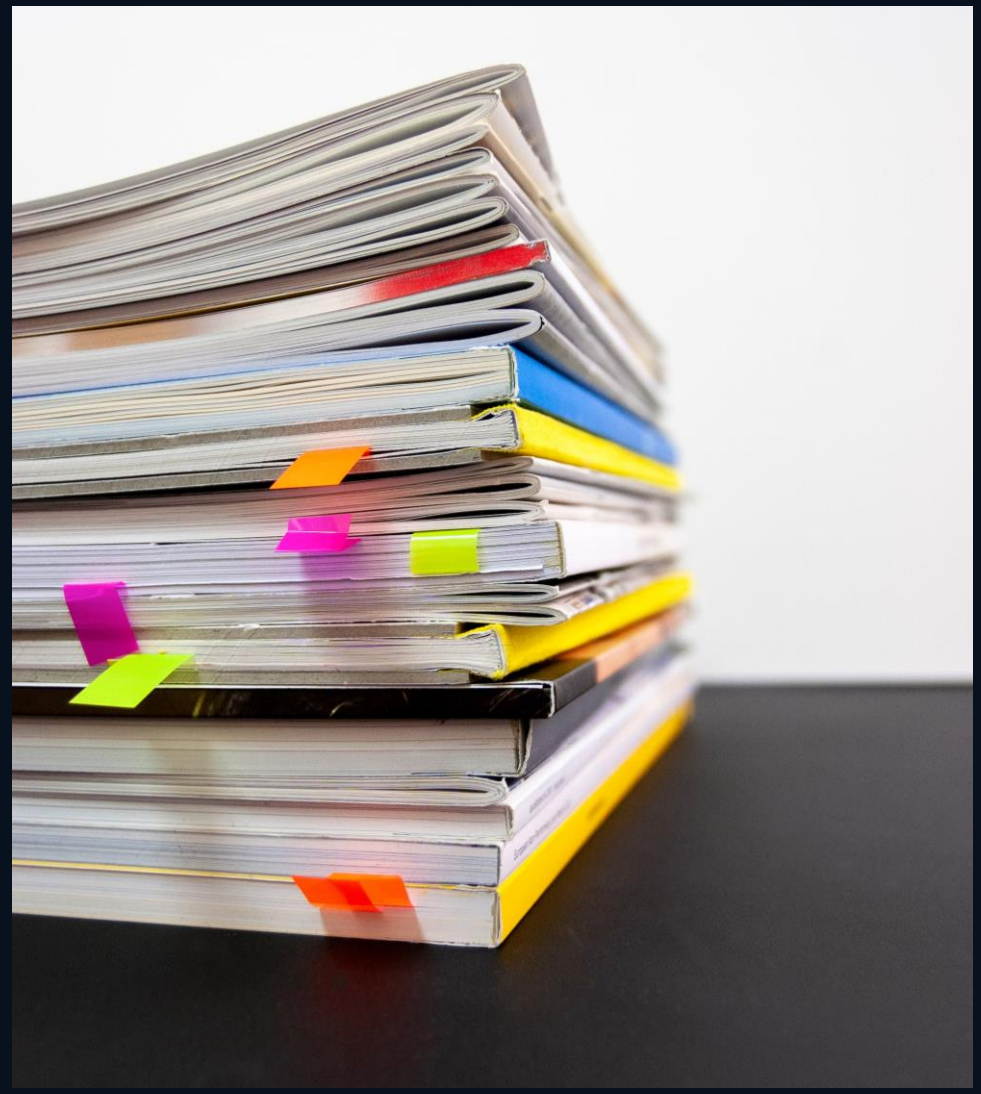


# Lesson Learned

A well-organized file ensures an efficient review

# Notified Body Expectations for Content of Technical Documentation



# File Content



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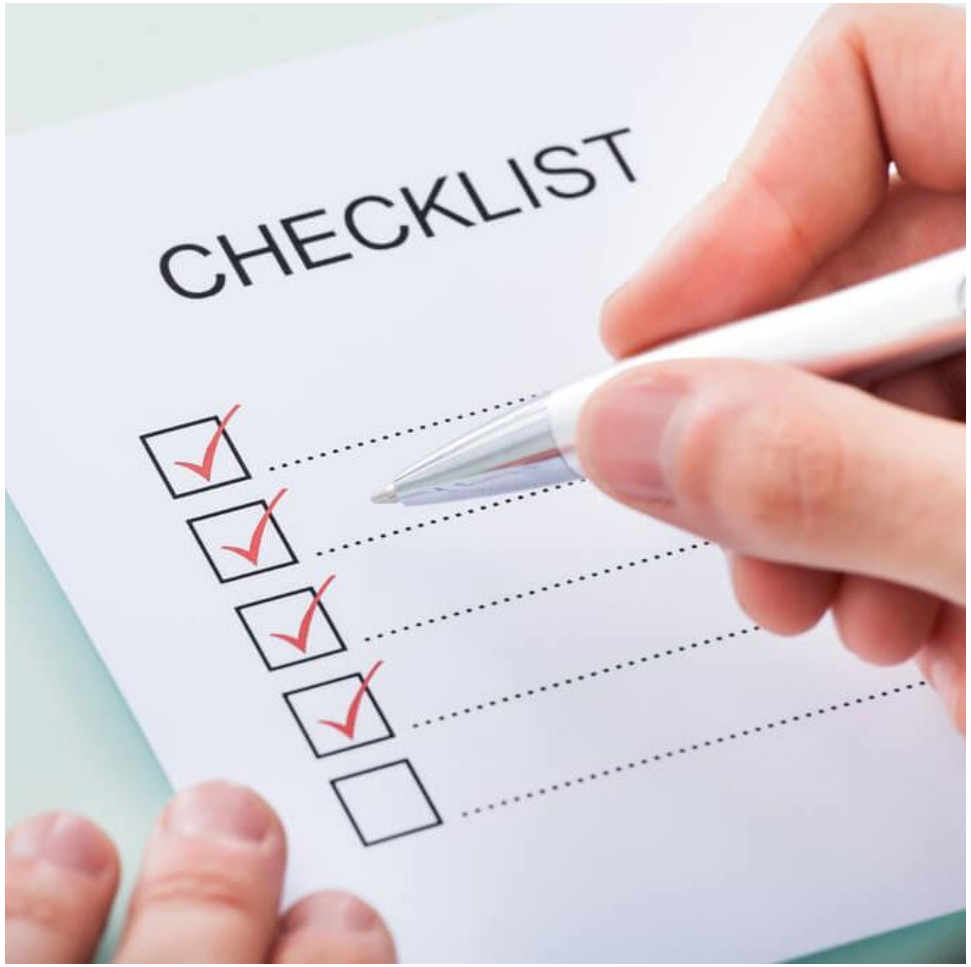


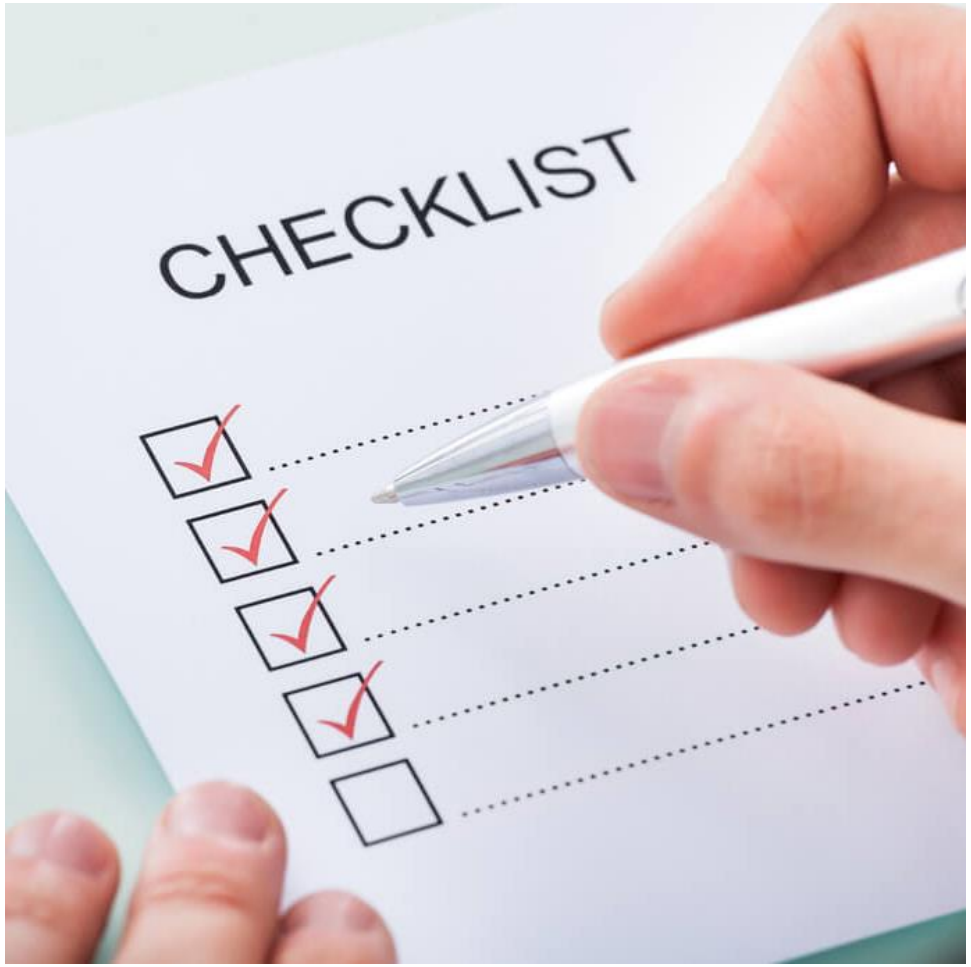
# Requirements of Annex II

Annex II provides a specific and detailed list of information required to be included in the technical documentation.

The technical documentation needs to address each individual item.

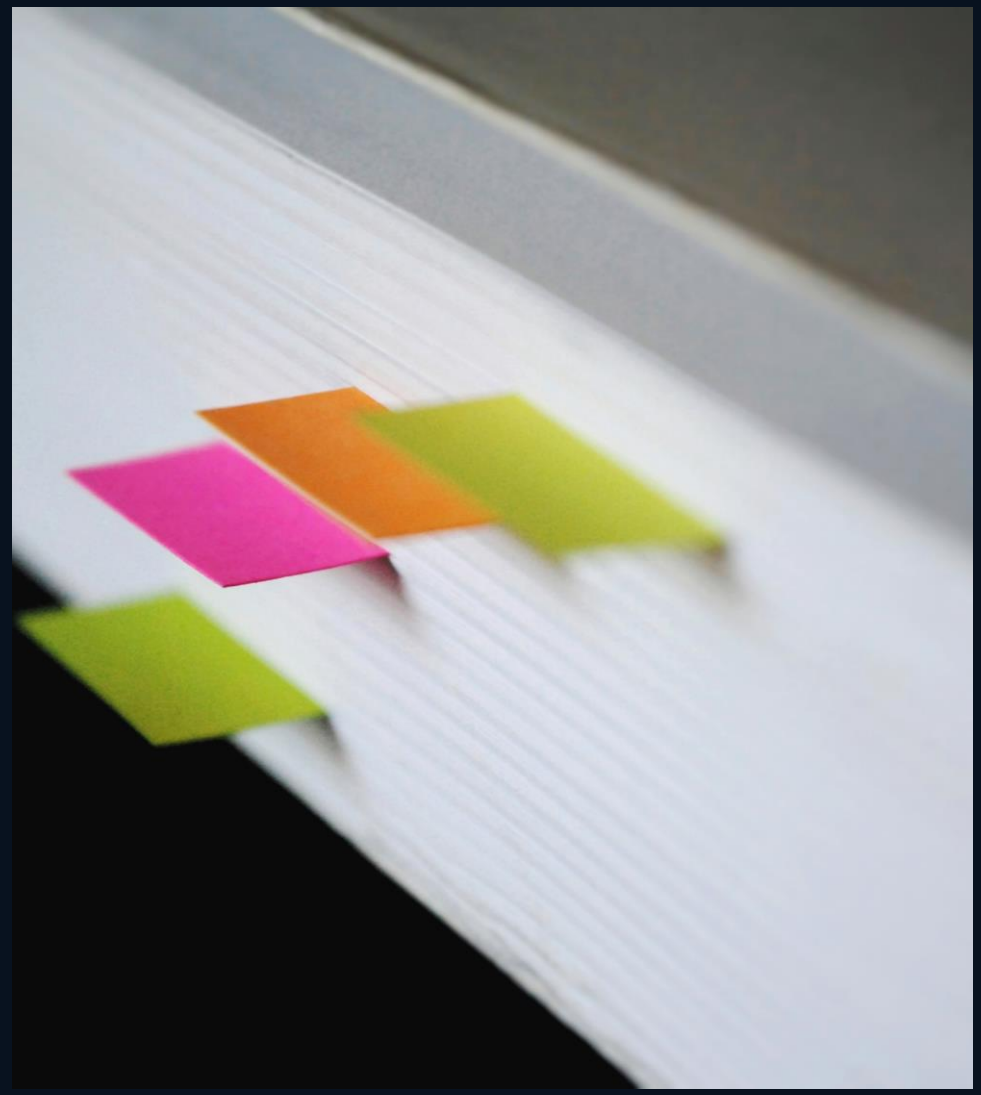
Where any item is not applicable, a justification is required.

**Even if it appears obvious based on the design or intended purpose of the device.**



# Some Specific Points

Items that have frequent issues



# Intended Purpose

The intended purpose needs to cover all points of Annex II Section 1.1 (c)

Preferably, all elements are covered directly in the intended purpose statement

It's acceptable to separate specific items from the intended purpose statement, provided that they are easily located

The Intended Purpose must be consistent across the technical documentation

1.1. Device description and specification

(a) product or trade name and a general description of the device including its intended purpose and intended users;

(b) the Basic UDI-DI as referred to in Part C of Annex VI assigned by the manufacturer to the device in question, as soon as identification of this device becomes based on a UDI system, or otherwise a clear identification by means of product code, catalogue number or other unambiguous reference allowing traceability;

(c) the intended purpose of the device which may include information on:

(i) what is to be detected and/or measured;

(ii) its function such as screening, monitoring, diagnosis or aid to diagnosis, prognosis, prediction, companion diagnostic;

(iii) the specific disorder, condition or risk factor of interest that it is intended to detect, define or differentiate;

(iv) whether it is automated or not;

(v) whether it is qualitative, semi-quantitative or quantitative;

(vi) the type of specimen(s) required;

(vii) where applicable, the testing population;

(viii) the intended user;

(ix) in addition, for companion diagnostics, the relevant target population and the associated medicinal product(s).

# Description of Components



Annex II Section 1.1 (g) requires the “description of the reactive ingredients such as antibodies, antigens, nucleic acid primers”

Include the source of antigen, antibody clone, *oligonucleotide sequences*

Where such information is proprietary, it’s not a requirement to make these public, but must be provided to the notified body for review

(viii) the intended user;

(ix) in addition, for companion diagnostics, the relevant target population and the associated medicinal product(s).

(d) the description of the principle of the assay method or the principles of operation of the instrument;

(e) the rationale for the qualification of the product as a device;

(f) the risk class of the device and the justification for the classification rule(s) applied in accordance with Annex VIII;

(g) the description of the components and where appropriate, the description of the reactive ingredients of relevant components such as antibodies, antigens, nucleic acid primers;

and where applicable:

# GSPRs

Annex II Section 4 requires (b) documentation of the methods used to demonstrate conformity and (d) “precise identity” of documents and location in the technical documentation

Simply citing the Risk Analysis as evidence of compliance is compliant with the requirement in (d) but doesn’t meet the requirement in (b)

Specify where within large documents evidence is found – e.g. Risk ID number

Make sure that documents referred to actually exist within the technical documentation

4. GENERAL SAFETY AND PERFORMANCE REQUIREMENTS

The documentation shall contain information for the demonstration of conformity with the general safety and performance requirements set out in Annex I that are applicable to the device taking into account its intended purpose, and shall include a justification, validation and verification of the solutions adopted to meet those requirements. The demonstration of conformity shall also include:

(a) the general safety and performance requirements that apply to the device and an explanation as to why others do not apply;

(b) the method or methods used to demonstrate conformity with each applicable general safety and performance requirement;

(c) the harmonised standards, CS or other solutions applied;

(d) the precise identity of the controlled documents offering evidence of conformity with each harmonised standard, CS or other method applied to demonstrate conformity with the general safety and performance requirements. The information referred to under this point shall incorporate a cross-reference to the location of such evidence within the full technical documentation and, if applicable, the summary technical documentation.

# Product Verification and Validation

Annex II Section 6

Any non-applicable performance characteristics must be justified

The reports required by Annex XIII are part of the technical documentation

Stability studies include conclusion and *claimed stability*

Additional information – recombinant components are substances of microbial origin

6.1. Information on analytical performance of the device

6.1.1. Specimen type

This Section shall describe the different specimen types that can be analysed, including their stability such as storage, where applicable specimen transport conditions and, with a view to time-critical analysis methods, information on the timeframe between taking the specimen and its analysis and storage conditions such *as* duration, temperature limits and freeze/thaw cycles.

6.1.2. Analytical performance characteristics

6.1.2.1. Accuracy of measurement

(a) Trueness of measurement

This Section shall provide information on the trueness of the measurement procedure and summarise the data in sufficient detail to allow an assessment of the adequacy of the means selected to establish the trueness. Trueness measures apply to both quantitative and qualitative assays only when a certified reference material or certified reference method is available.

(b) Precision of measurement

This Section shall describe repeatability and reproducibility studies.

6.1.2.2. Analytical sensitivity

This Section shall include information about the study design and results. It shall provide a description of specimen type and preparation including matrix, analyte levels, and how levels were established. The number of replicates tested at each concentration shall also be provided as well as a description of the calculation used to determine assay sensitivity.

6.1.2.3. Analytical specificity

This Section shall describe interference and cross reactivity studies performed to determine the analytical specificity in the presence of other substances/agents in the specimen.

# Post-market Surveillance

Include effective and appropriate methods and processes to assess the collected data

Include methods to communicate with competent authorities, notified bodies, economic operators and users.

Specify indicators and thresholds to use in re-assessing the benefit-risk analysis and risk management.

Specify how each point of Article 78.3 is addressed

PMPF plan or justification – more on the next slide

PSUR or PMS Report – not required for new applications, but needs to be included once available

3. Data gathered by the manufacturer's post-market surveillance system shall in particular be used:

(a) to update the benefit-risk determination and to improve the risk management as referred to in Chapter I of Annex I;

(b) to update the design and manufacturing information, the instructions for use and the labelling;

(c) to update the performance evaluation;



(d) to update the summary of safety and performance referred to in Article 29;

(e) for the identification of needs for preventive, corrective or field safety corrective action;

(f) for the identification of options to improve the usability, performance and safety of the device;

(g) when relevant, to contribute to the post-market surveillance of other devices; and

(h) to detect and report trends in accordance with Article 83.

# A Word about PMS and PMPF



PMS is the process of routinely assessing the continued performance and safety of the device

PMPF is intended to address specific gaps in the clinical evidence.

The PMPF plan should describe what specific aspect of the device's performance it aims to address.

If available clinical evidence is sufficient, a PMPF plan is not needed.

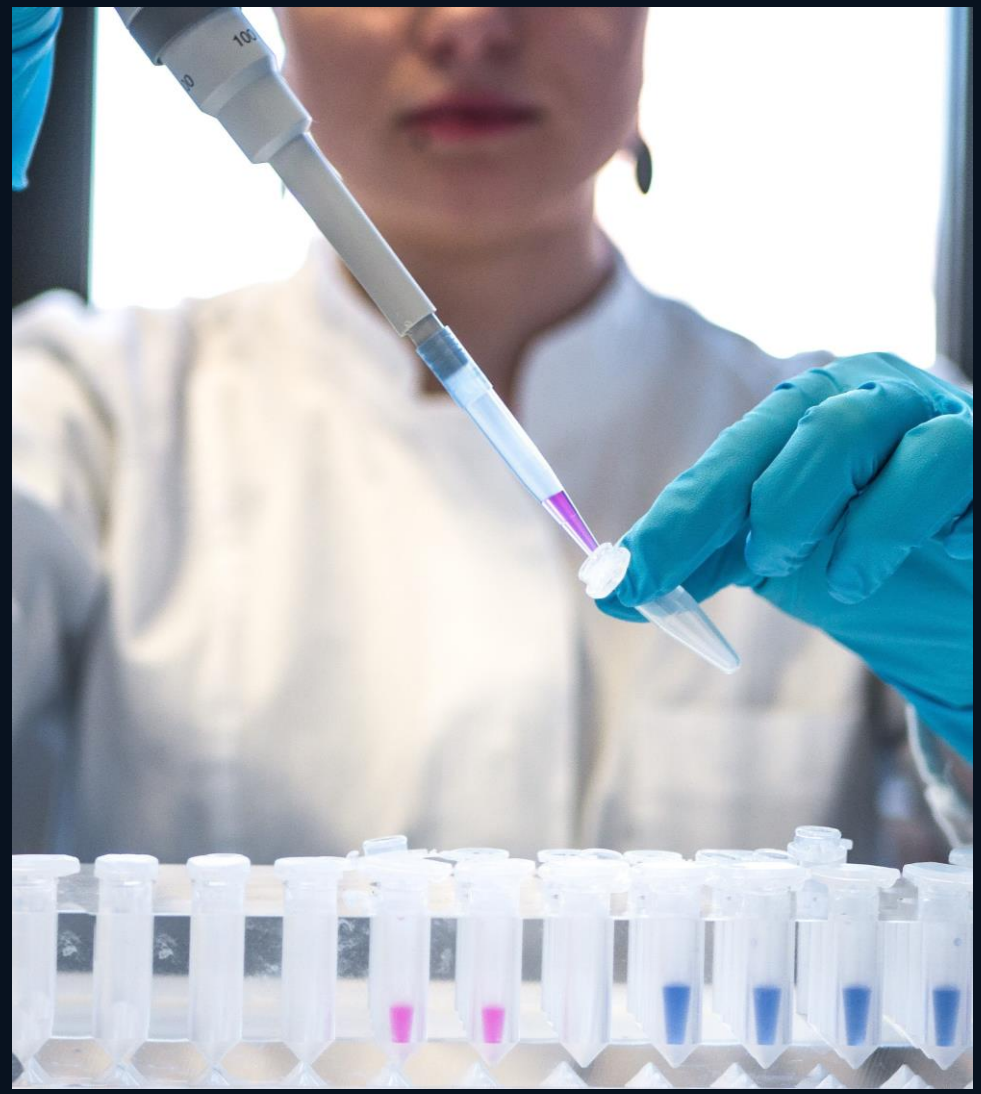
**Justification is required.**

# Lesson Learned

Every requirement must be addressed
Non-applicability must be justified

# Performance Evaluation

Annex XIII



# Performance Evaluation Plan

Required content: Each point must be addressed or justified

Ensure that all performance characteristics listed in Annex I Section 9 (c) **and** Section 20.4.1 are addressed

Specify which GSPRs will be addressed by the performance evaluation

1.1. Performance evaluation plan

As a general rule, the performance evaluation plan shall include at least:

— a specification of the intended purpose of the device;

— a specification of the characteristics of the device as described in Section 9 of Chapter II of Annex I and in point (c) of Section 20.4.1. of Chapter III of Annex I;

— a specification of the analyte or marker to be determined by the device;

— a specification of the intended use of the device;

— identification of certified reference materials or reference measurement procedures to allow for metrological traceability;

— a clear identification of specified target patient groups with clear indications, limitations and contra-indications;

— an identification of the general safety and performance requirements as laid down in Sections 1 to 9 of Annex I that require support from relevant scientific validity and analytical and clinical performance data;

— a specification of methods, including the appropriate statistical tools, used for the examination of the analytical and clinical performance of the device and of the limitations of the device and information provided by it;

— a description of the state of the art, including an identification of existing relevant standards, CS, guidance or best practices documents;

# State of the Art



Describe the state of the art *in medicine* for the device intended purpose

How is the specific condition, disease, etc. currently diagnosed in routine medical practice?

Look beyond the technology of ‘your’ device.

State of the art is not necessarily the latest and greatest new development, but what is current practice.

A list of current standards is not sufficient.

Guidance from regulatory agencies or best practice documents from relevant professional organism related to the disease/condition.

1.1. Performance evaluation plan

As a general rule, the performance evaluation plan shall include at least:

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— a specification of the analyte or marker to be determined by the device;

— a specification of the intended use of the device;

— identification of certified reference materials or reference measurement procedures to allow for metrological traceability;

— a clear identification of specified target patient groups with clear indications, limitations and contra-indications;

— an identification of the general safety and performance requirements as laid down in Sections 1 to 9 of Annex I that require support from relevant scientific validity and analytical and clinical performance data;

— a specification of methods, including the appropriate statistical tools, used for the examination of the analytical and clinical performance of the device and of the limitations of the device and information provided by it;

— a description of the state of the art, including an identification of existing relevant standards, CS, guidance or best practices documents;

# Performance Evaluation Plan continued



Specify how the benefit-risk ratio and its acceptability will be determined

Think about how to quantify benefit.

When describing product development phases, specify when and how scientific validity, analytical and clinical performance are determined

Describe PMPF planning or justify if no PMPF is needed

— an indication and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the intended purpose or purposes and for the analytical and clinical performance of the device;

— for software qualified as a device, an identification and specification of reference databases and other sources of data used as the basis for its decision making;

— an outline of the different development phases including the sequence and means of determination of the scientific validity, the analytical and clinical performance, including an indication of milestones and a description of potential acceptance criteria;

— the PMPF planning as referred to in Part B of this Annex.

Where any of the above mentioned elements are not deemed appropriate in the Performance Evaluation Plan due to the specific device characteristics a justification shall be provided in the plan.

# Literature review



Regardless of what other means are used to establish scientific validity and analytical and clinical performance, a review of the literature is required

Methodology, protocol and report to be included in the performance evaluation report

More than one search may be needed to establish state of the art, scientific validity, and/or aspects of performance

Ensure that the search is designed to reveal potential unfavorable data, and discuss any such unfavorable data in the literature search report and performance evaluation report

1.2. Demonstration of the scientific validity and the analytical and clinical performance:

As a general methodological principle the manufacturer shall:

— identify through a systematic scientific literature review the available data relevant to the device and its intended purpose and identify any remaining unaddressed issues or gaps in the data;

— appraise all relevant data by evaluating their suitability for establishing the safety and performance of the device;

— generate any new or additional data necessary to address outstanding issues.

# Scientific validity

Scientific validity describes the association of the analyte or marker with the disease/condition.

At least one of the listed methods must be used.

For well-established markers, there is typically adequate literature or consensus opinions

For new markers, proof of concept studies may be needed

For devices with multiple or broad claims, scientific validity is required to cover all claims

1.2.1. Demonstration of the scientific validity

The manufacturer shall demonstrate the scientific validity based on one or a combination of the following sources:

— relevant information on the scientific validity of devices measuring the same analyte or marker;

— scientific (peer-reviewed) literature;

— consensus expert opinions/positions from relevant professional associations;

— results from proof of concept studies;

— results from clinical performance studies.

The scientific validity of the analyte or marker shall be demonstrated and documented in the scientific validity report.

# Analytical Performance

Address each point of Annex I Section 9.1 (a) or justify

If justification is in another document, provide a reference to its location

Be sure to include the pre-defined acceptance criteria for each study

Clearly describe the performance claims resulting from the analytical performance studies

1.2.2. Demonstration of the analytical performance

The manufacturer shall demonstrate the analytical performance of the device in relation to all the parameters described in point (a) of Section 9.1 of Annex I, unless any omission can be justified as not applicable.

As a general rule, the analytical performance shall always be demonstrated on the basis of analytical performance studies.

For novel markers or other markers without available certified reference materials or reference measurement procedures, it may not be possible to demonstrate trueness. If there are no comparative methods, different approaches may be used if demonstrated to be appropriate, such as comparison to some other well-documented methods or the composite reference standard. In the absence of such approaches, a clinical performance study comparing performance of the novel device to the current clinical standard practice is required.

Analytical performance shall be demonstrated and documented in the analytical performance report.

# Clinical Performance



At least one of the listed approaches must be used

Older clinical investigations (e.g. for IVDD or FDA submission) do not typically qualify as clinical performance studies under IVDR

They are admissible as “other sources” of clinical performance data, but one of the listed approaches is still required.

Consider the age of the clinical data to ensure that they are still in line with the state of the art.

1.2.3. Demonstration of the clinical performance

The manufacturer shall demonstrate the clinical performance of the device in relation to all the parameters described in point (b) of Section 9.1. of Annex I, unless any omission can be justified as not applicable.

Demonstration of the clinical performance of a device shall be based on one or a combination of the following sources:

— clinical performance studies;

— scientific peer-reviewed literature;

— published experience gained by routine diagnostic testing.

Clinical performance studies shall be performed unless due justification is provided for relying on other sources of clinical performance data.

Clinical performance shall be demonstrated and documented in the clinical performance report.

# Performance Evaluation Report



Include the SVR, APR and CPR – may be by reference to the separate reports

Justify the approach taken – how is the evidence collected sufficient to support performance and safety?

Specify the performance claims and how they are supported by the clinical evidence.

How is the demonstrated performance in line with the state of the art?

1.3.2. Performance evaluation report

The clinical evidence shall be documented in a performance evaluation report. This report shall include the scientific validity report, the analytical performance report, the clinical performance report and an assessment of those reports allowing demonstration of the clinical evidence.

The performance evaluation report shall in particular include:

— the justification for the approach taken to gather the clinical evidence;

— the literature search methodology and the literature search protocol and literature search report of a literature review;

— the technology on which the device is based, the intended purpose of the device and any claims made about the device's performance or safety;

— the nature and extent of the scientific validity and the analytical and clinical performance data that has been evaluated;

— the clinical evidence as the acceptable performances against the state of the art in medicine;

— any new conclusions derived from PMPF reports in accordance with Part B of this Annex.

# Performance Evaluation Report continued

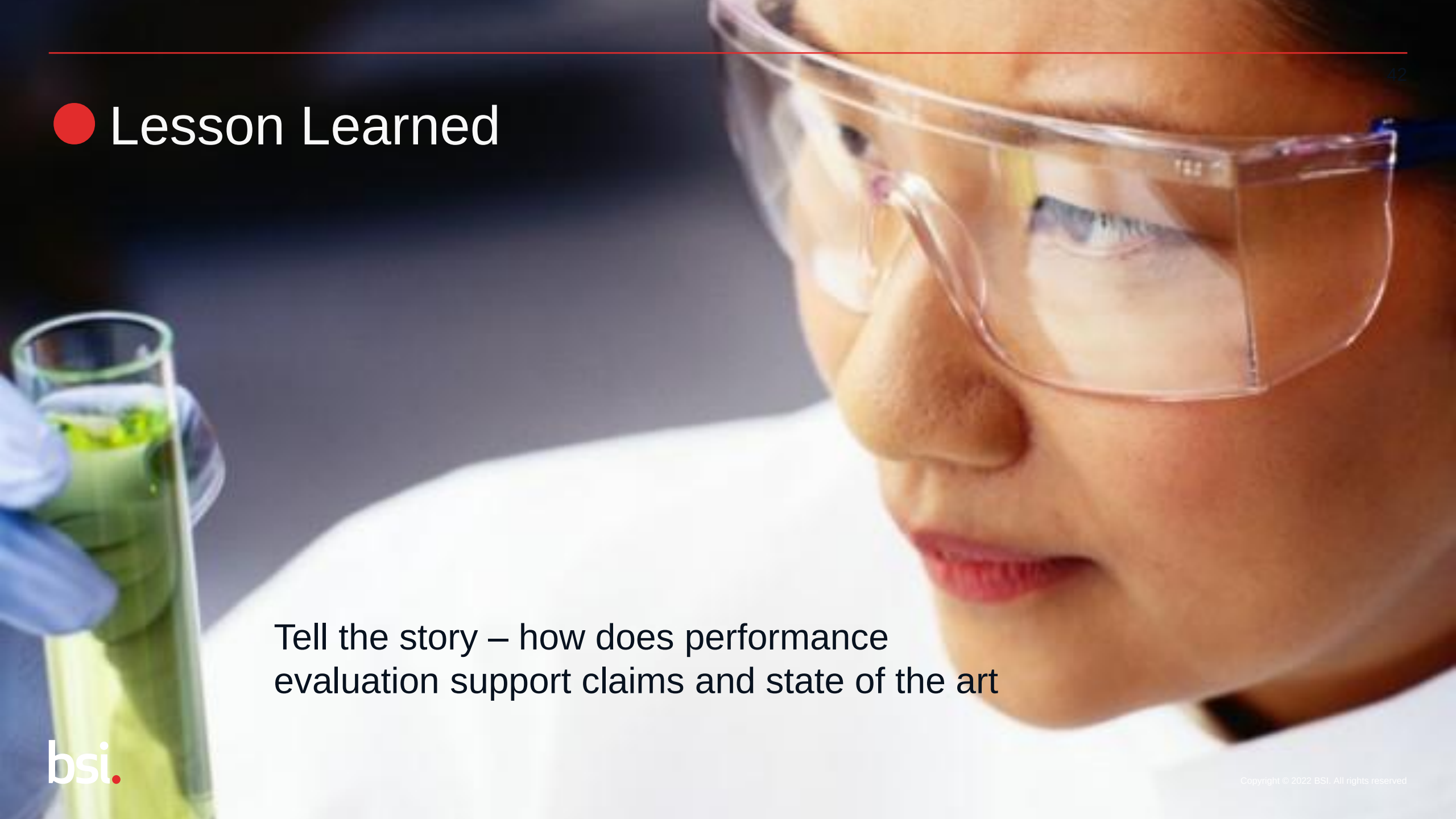
Describe how the report will be updated throughout the device life cycle.

Link to processes that may reveal new information – risk management, PMS, PMPF

Ensure that favorable and unfavorable data are considered and describe how any unfavorable data impact the benefit-risk analysis.

1.3.3. The clinical evidence and its assessment in the performance evaluation report shall be updated throughout the life cycle of the device concerned with data obtained from the implementation of the manufacturer's PMPF plan in accordance with Part B of this Annex, as part of the performance evaluation and the post-market surveillance system referred to in Article 10(9). The performance evaluation report shall be part of the technical documentation. Both favourable and unfavourable data considered in the performance evaluation shall be included in the technical documentation.

# Lesson Learned



Tell the story – how does performance evaluation support claims and state of the art

# SSP – Class C & D

Information in the SSP must be consistent with the IFU and performance evaluation

Harmonized standards – include standards already harmonized to the IVDR and any other state of the art standards applied

The summary of the performance evaluation must be comprehensive – the SSP is a stand-alone document and needs to allow the reader to understand the performance of the device

There is no current guidance on the content of the SSP, but MDCG 2019-9 on the SSCP for MDR gives an idea of what to expect for future SSP guidance.

2. The summary of safety and performance shall include at least the following aspects:

(a) the identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN;

(b) the intended purpose of the device and any indications, contra-indications and target populations;

(c) a description of the device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other devices and products, which are intended to be used in combination with the device;

(d) reference to any harmonised standards and CS applied;

(e) the summary of the performance evaluation as referred to in Annex XIII, and relevant information on the PMPF;

(f) the metrological traceability of assigned values;

(g) suggested profile and training for users;

(h) information on any residual risks and any undesirable effects, warnings and precautions.

# Thank you