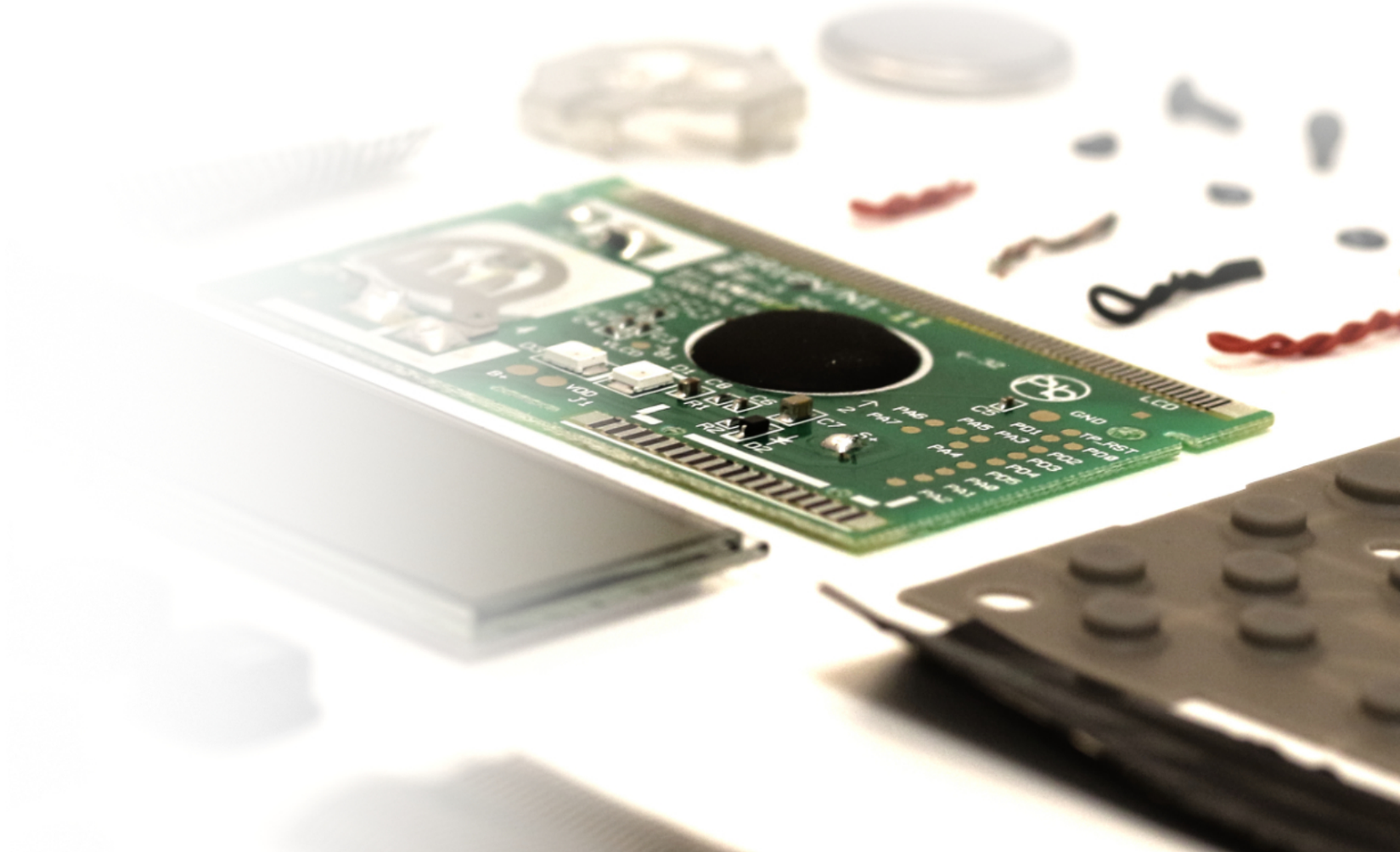
Claigan
Less Journey. More Results.

Claigan Webinar - EU MDR Justification Document

A practical walkthrough - with detailed examples



Presented by:
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February 26, 2026

Overview - Agenda

- EU MDR / Cat 1 CMRs
  - Cobalt and NMP
- 10.4.2 Justification
  - Guidance
  - Notified body approach
- 10 Sections of a Justification Doc.
  - With details
  - And examples
- A brief conversation on allergens
- Summary
- Q&A

What is an EU MDR Justification Document?

- **EU Medical Device Regulation (EU MDR)**

- **Section 10.4 - Substances**
  - Cat 1 Carcinogens, Mutagens, Reproductive Toxins (CMRs)
  - >0.1% w/w
  - In an invasive, fluid, or gas path
  - Are required to
    - Label
    - Justify the presence of the CMR

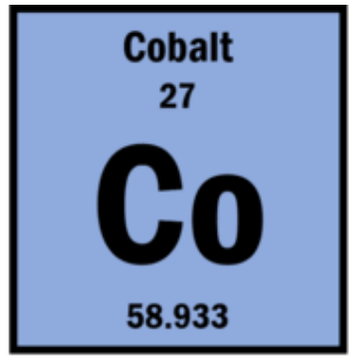
Why do **most** invasive devices need EU MDR Justification Documents

- **Historically**
  - DEHP in fluid path
  - Pb in brass in air path
  - <5% of invasive / fluid path medical devices

- **Now**
  - New CMRs
    - Cobalt in stainless steel
    - NMP in polyimide coatings
  - ~50% of invasive/ fluid path medical devices

Cobalt in Stainless

- **Cobalt**
  - Became a Cat 1 CMR October 1, 2021



- **Occurrence in medical devices**
  - Present in >99% of stainless steel parts
    - And normally above >0.1%

- The most common CMR over 0.1% in invasive path

NMP in Polyimide

- **NMP**
  - Has been a cat 1 CMR since August 10, 2009

- **Occurrence in medical devices**
  - The primary solvent in polyimide coating
    - Is present in >99% of polyimide materials in medical devices
    - Is routinely present between 500 and 1,500 ppm

- The most common ‘unknown’ CMR in medical devices

10.4.2 Justification (EU MDR)

- **The justification for the presence of such substances shall be based upon:**

  a. an analysis and estimation of potential patient or user exposure to the substance;

  b. an analysis of possible alternative substances, materials or designs, including, where available, information about independent research, peer-reviewed studies, scientific opinions from relevant scientific committees and an analysis of the availability of such alternatives;

  c. argumentation as to why possible substance and/ or material substitutes, if available, or design changes, if feasible, are inappropriate in relation to maintaining the functionality, performance and the benefit-risk ratios of the product; including taking into account if the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials; **and**

10.4.2 Justification (EU MDR)

- **and**

  d. where applicable and available, the latest relevant scientific committee guidelines in accordance withSections 10.4.3. and 10.4.4.

- Section 10.4.3
  - Phthalates guidance

- Section 10.4.4
  - Other guidances (as they appear)

EU MDR Justification Document Main Guidance

- **SCHEER update 17 June 2024**
  - *Update of the Guidelines on the benefit-risk assessment of the presence of phthalates in certain medical devices covering phthalates which are carcinogenic, mutagenic, toxic to reproduction (CMR) or have endocrine-disrupting (ED) properties*
  - Includes the Framework for Benefit Risk Assessment

EU MDR Justification Document Understanding the Notified Body 'Ask'

- **Notified body rules**
  - ***Team-NB Position Paper***
  - *Best Practice Guidance for the Submission of Technical Documentation under Annex II and III of Medical Device Regulation (EU) 2017/745*
  - *p. 47*

This is what a notified body with check for

And what we will talk about for the rest of the webinar

Please provide the following data:

- Applicability of CMR substances (carcinogenic, mutagenic or toxic to reproduction) substances having endocrine disrupting properties in a concentration of > 0.1% w/w acc. to GSPR 10.4.1.

- List substances in a concentration of > 0.1% w/w.

- If evidence is based on published literature, manufacturers should rationalise the applicability of such literature data to their own device considering the nature of their device, intended purpose, contact with various body tissues and other substances etc. Or provide planning and overview as well as reports of tests performed, evaluation of data and test results.

- Justification according to GSPR 10.4.2 for use of substances in a concentration of > 0.1% w/w including:
  - An analysis and estimation of potential patient or user exposure to the substance.
  - An analysis of possible alternative substances, materials or designs, including, when available, information about independent research, peer reviewed studies, scientific opinions from relevant Scientific Committees and an analysis of the availability of such alternatives.
  - Argumentation because possible substance and/ or material substitutes or design changes, if available, are inappropriate to maintain the functionality, performance and the benefit-risk ratios of the product; including considering if the intended use of such devices includes treatment of children or treatment of pregnant or nursing women or treatment of other patient groups considered particularly vulnerable to such substances and / or materials.
  - Where applicable and available, the latest relevant Scientific Committee guidelines (as per GSPR 10.4.3 and 10.4.4).

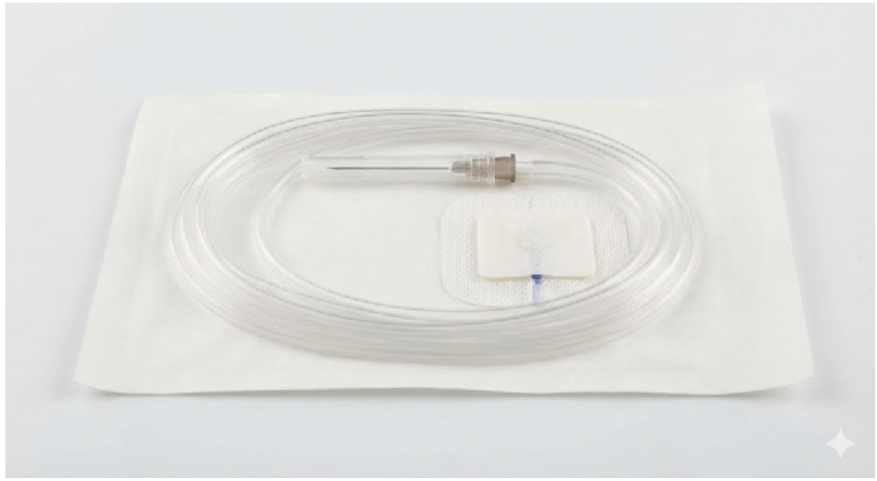
- Copy of labelling including the list of such substances in a concentration of > 0.1% w/w on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging.

- Copy of IFU: If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures is given in the instructions for use.

Note: a process to identify and regularly update CMR or endocrine disrupting substances using relevant standards: CLP regulation + ATPs (Adaption to Technical Progress), ECHA webpage, REACH, SVCH list, Commission Delegated Regulation (EU) 2017/2100, SCHEER guideline refers to ECHA's endocrine disruptor (ED) assessment list and ECHA list for Biocidal Products Committee opinions on active substances will be part of an audit.

Section 1 - Description and Characterization

- **Example product**
  - Infusion pump
    - Stainless steel needle



- CMR
  - Cobalt in the stainless steel
    - Invasive & fluid contact component w/ CMR

Questions - Description and Characterization

- What is the purpose of the *device*?
    - This section usually matches marketing and IFU language
- What procedure(s) does it support?
- Which invasive and/or fluid-contacting *components* contain CMRs?
    - What is their purpose?
    - What is the substrate material?
    - What is the concentration of the CMR in the substrate material and how is it "bound" in it? ***Why*** is the CMR there?
    - With which media do they come into contact and for how long?

Section 2 -
Use and Function

- **Example product**
  - Microcatheter
  - Coating on microcatheter

- CMR
  - NMP in polyimide catheter coating
  - Invasive CMR

Questions - Use and Function

- What are the characteristic design requirements for the component?
  - material strength, flexion, friction reduction, sterilization compatibility, machinability, tolerances, chemical stability, bonding, marking, radioopacity/ luscence, biocompatibility
  - How are the requirements met by the currently used material?
- What are the medical benefits of the device, component, and/ or material?
  - What medical procedures are supported?
  - How are these of benefit?
  - What patient population do they benefit?

Section 3 - Assessment of Risk

- **Example product**
  - Trocar
  - Stainless steel trocar

- CMR
  - Cobalt in stainless steel
  - Invasive CMR

Questions -
Assessment of Risk - (1) *Literature Review*

- What are the toxicological risks documented in literature associated with exposure to the CMR, at what dose?
- Is there background environmental exposure to the CMR?
- Are there literature sources for migration rates of the CMR from similar materials, substances, media, and applications?
- Are there published allowable daily levels of exposure to the CMR?
    - Are there scaling factors required for critical treatment populations?

Questions -
Assessment of Risk - (2) *Direct Testing*

- Who is patient population for the device? (Match with the IFU and known uses for your device)
  - Does it include pregnant / nursing women?
  - Does it include children?
  - Does your IFU include contraindications for use?
- What media does your component material come into contact with?
  - What is the surface area of exposure?
  - What is the duration of exposure?
  - Do you have clinically-relevant migration test results for the material/ component?
- How does the exposure compare to daily allowable exposures?

Section 4 - Assessment of **Possible** Alternatives

- **Example product**
  - Heating element in ventilator humidification system
  - Stainless steel heating element
- CMR
  - Cobalt in stainless steel heating element
  - Gas path CMR

Questions - Assessment of **Possible** Alternatives

- **Assessment of possible alternatives for**
  - Substances
    - *cobalt*
  - Materials
    - *Stainless steel*
  - Designs
    - *How the device works*
  - Procedures
    - *Other procedures*

- **Note -** this is about what is possible not necessarily what is effective

Questions - Assessment of **Possible** Alternatives

- **Substances**
  - What substances could be used to achieve the same purpose?
- **Materials**
  - Are there other specific materials or material families that could be used that do not contain the CMR substance?
    - Are any of your competitors using a different material to achieve the same purpose?
- **Design**
  - Could the design be changed to reduce or eliminate the exposure to the substance, or make the use of an alternative material/substance possible?
- **Procedure**
  - Is there a different approach that could offer the same medical outcome?

Section 5 - Assessment of **Relevant** Alternatives

- **Example product**
  - Dental files (root canal)
  - Stainless steel file

- CMR
  - Cobalt in stainless steel file
  - Invasive CMR

Questions - Assessment of **Relevant** Alternatives

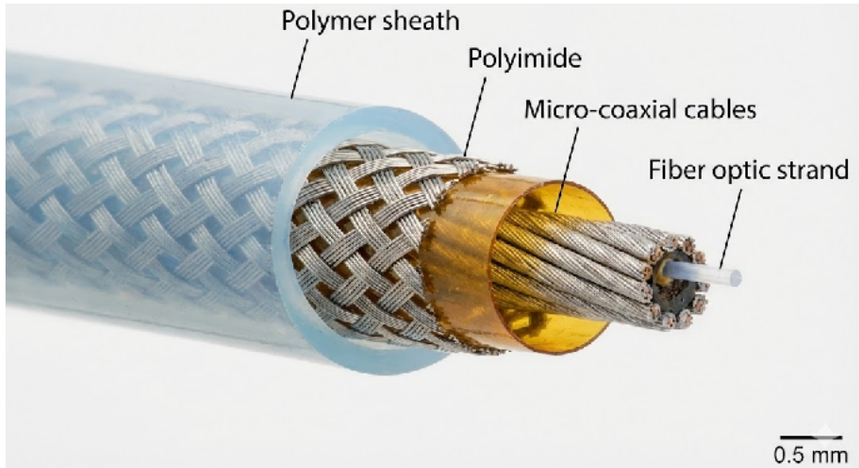
- **Consider basic functional requirements which of the broad list of alternative substances are <u>relevant</u> to the application?**

- **Substances**
  - If the substance is present as a contaminant and does not impact material properties, there may be no relevant alternative to discuss

- **Materials:**
  - Which are the materials from the broad list that could be considered for this application?
- **Design**
  - Which design changes could be made without introducing additional risks to patients (either chemical or physical)?
- **Procedure**
  - Have any of the alternative procedures proposed proven too risky to consider?

Section 6 - Description of Identified Alternatives & Feasibility

- **Example product**
  - Imaging catheter
  - Polyimide coating



- CMR
  - NMP in catheter coating
  - Invasive CMR

Questions - Description of Identified Alternatives & Feasibility

- For each **relevant** alternative:
  - Is the use of the alternative technologically feasible?
  - Is the alternative commercially available?
  - Are there unknowns that need to be answered?
  - What timeframe would be required for research and development with the alternative?
  - Are there equivalent risks associated with the alternative?
    - For example - an alternative procedure would have to continue to use the current material for other aspects of it?

Section 7 - Assessment of Risk of Relevant Alternatives

- **Example product**
  - Fistula needle
  - Stainless steel needle

- CMR
  - Cobalt in stainless steel needle
  - Invasive CMR

Questions - Assessment of Risk of Relevant Alternatives

- What are the chemical, biological, and physical **risks** associated with alternative substances, materials, designs & procedures?

- Is there an allowable daily exposure for each alternative substance?
    - For each alternative substance / substances contained in an alternative material with an allowable daily exposure,
        - Calculate the margin of safety based on relative leachability, concentration in comparison with the current substance.

Section 8 - Comparison of Functionality and Performance

- **Of Relevant Alternatives**

- **Example product**
  - Urinary stone retrieval device
  - Polyimide coated

- CMR
  - NMP in polyimde coating
  - Invasive CMR

Questions - Comparison of Functionality and Performance

- Revisit the table of functional requirements for the device component (biocompatibility, mechanical properties, etc.) for each feasible alternative.
  - Does the alternative meet or exceed the functional requirement of the device / component / procedure?
  - Does the alternative provide or exceed the medical benefit of the current substance / material / design / procedure?
  - If unknown, how long would it take to determine?

Section 9 - Comparison of Risk of CMR with Alternatives

- **Example product**
  - Pre-Fillable Syringe
  - Stainless steel needle

- CMR
  - Cobalt in stainless steel needle
  - Invasive CMR

Questions - Comparison of Risk of CMR with Alternatives

- How do the margins of safety of the feasible alternatives compare with the current substance, material, design or procedure?

- What other physical (e.g. particulate), biological (e.g. infection), or chemical (e.g. environmental impact, sensitizer) risks are associated with the feasible alternatives?

Typical Exposure Tests

- **Many focus on ISO 10993-17 (tox. risk) and ISO 10993-18 (chem. char.), but these may not provide clinically relevant data for exposure calculations. Consider additional simple migration tests based on clinical use parameters.**
  - For exposure calculations, migration tests should focus on device parts that are actually invasive or on the fluid (or gas) path
    - If the test is providing a total migration measurement (i.e. µg), is the test limited to only those surfaces that are in direct invasive, and indirect invasive fluid path?
    - Test sensitivity is critical. Remember: ND ≠ 0, ND = LOD or LOQ of test!
- **Simulant medium:**
  - Based on the media with which the component will come into contact and the factors that represent the realistic worst-case solvent characteristics for the substance of concern
- **Time and Temperature:**
  - Time and temperature should be relevant to the worst-case clinical experience, but **time** may require exaggeration to achieve required test sensitivity.
    - BUT migration is likely not linear!

Typical Exposure Tests

- **Cobalt Example**
  - **Device**: Syringe
  - **Component**: Cobalt-containing 300-series stainless steel needle, 22 gauge, 16 mm
  - **Intended use**: Administration of insulin for type 1 diabetes
  - **Vulnerable Patient**: 6-month old infant, 7.8 kg (ATSDR)
  - **Contact**: invasive and fluid contact - transdermal with blood (pH typically 7.4), tissues, and insulin (pH Humulin = 7.0-7.8)
  - **Frequency, duration, surface area of contact**: 2 times per day, 7 days per week, <1 minute, 0.557 cm^2

Needle Gauge Chart

(From: internationalfilterproducts.com)

- **Migration Test Parameters**
  - Needle, immersion, purified water (pH 7.0 - ISO 10993-18) or Phosphate buffered saline (pH 7.4), 37°C, 24 hours, LOD_{max} 0.05 $\mu g/cm^2/day$

Example Exposure Calculations

Parameter	Value	Units
Migration in 24 hours (Result = ND)	0.05	µg/cm²/day
Surface Area of contact	0.56	cm²
Cobalt migration in 24 hours	0.28	µg/day
	Assuming all cobalt migrates immediately (worst-case)	
# procedures / day	2	/day
Cobalt exposure per day	0.056	µg/day
Patient body weight	7.8	kg
Patient exposure / kg-bw	0.0072	µg/kg-bw/day
Most sensitive endpoint (cancer)	8.9	µg/kg-bw/day
Margin of Safety	1200	

Section 10 - Comparison of Benefit and Risk

- **Of CMR with potential alternatives**

- **Example product**
  - Glucose monitor
  - Stainless steel needle
  - Polyimide coated sensor

- CMR
  - Cobalt in stainless steel
  - NMP in polyimide coating
    - Invasive CMRs

Questions - Comparison of Benefit and Risk

- What are the margins of safety associated with each alternative compared with the current substance?

- What are the medical benefits and risks associated with each alternative compared with the current substance?

- What are the modes of failure and potential medical outcomes associated with each alternative compared with the current substance and the functional criteria for the device and component?

Reminder
Most Invasive Medical Devices have CMRs

- **Historically**
  - DEHP in fluid path
  - Pb in brass in air path
  - <5% of invasive / fluid path medical devices

- **Now**
  - New CMRs
    - Cobalt in stainless steel
    - NMP in polyimide coatings
  - **~50% of invasive/ fluid path medical devices**

Allergen Reminders

- **Allergens**
  - Warnings are required under 23.4s
  - Most likely source of enforcement
    - People react immediately to allergens
    - Visual evidence

- **Many medical devices companies are unaware of the most common allergens**
    - Mostly because the ‘sensitization tests’ are not applicable to most allergens

Most Common Allergens

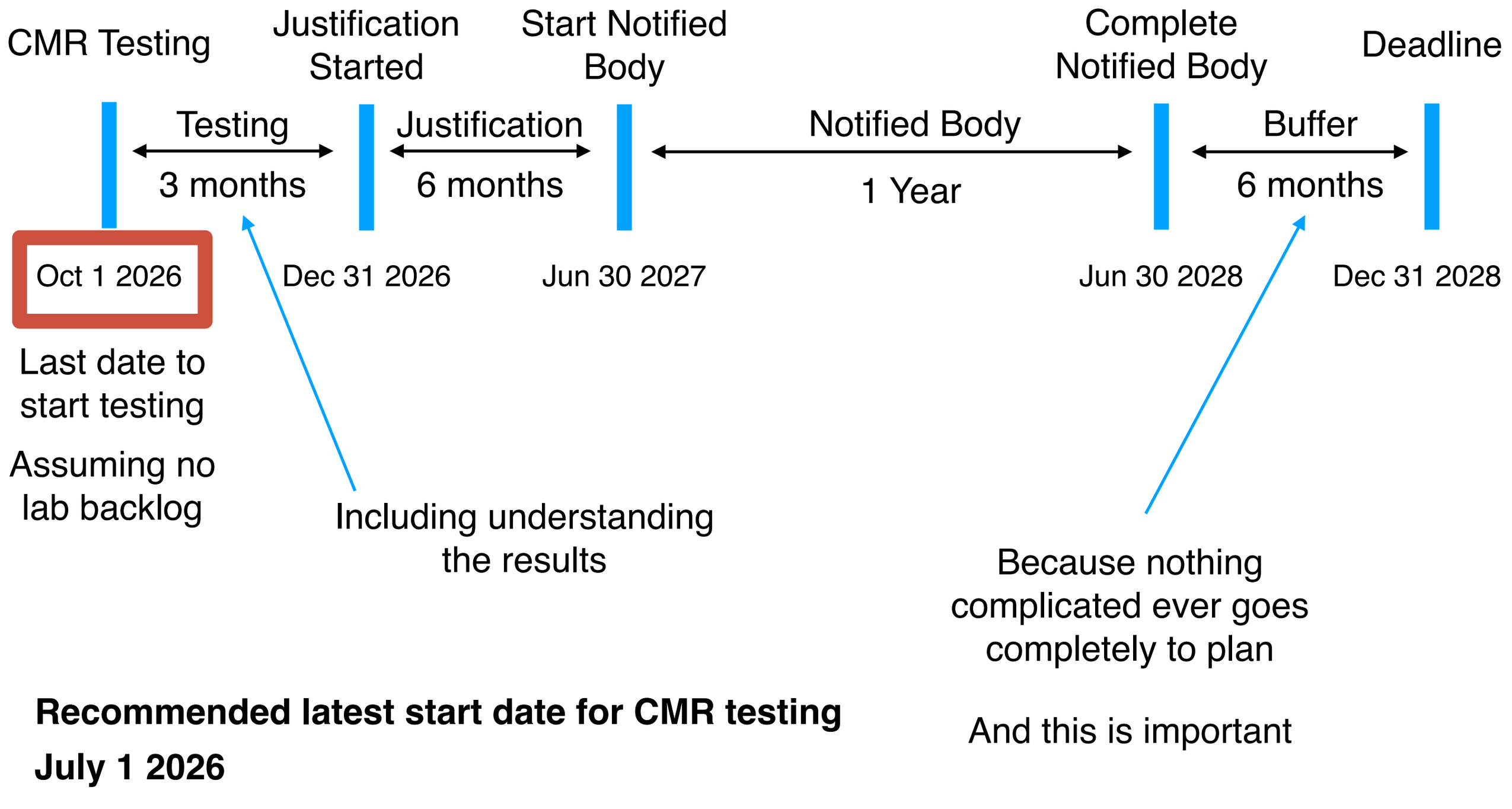
- **In medical devices**
  - Acrylate monomers in PMMA
  - Acrylate monomers in adhesives
  - Nickel
  - Cobalt

- **Have you tested with anything but 'out-of-date' sensitization tests?**
  - No?
  - Then set aside some money for legal action.
    - Because **NONE** of the old tests for sensitization work for acrylates, nickel, or cobalt

Water vs sweat oil transport

Missing toll-like receptor 4

EU MDR
CMR according to 10.4



Recommended latest start date for CMR testing

July 1 2026

Why do **most** invasive devices need EU MDR Justification Documents

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Q&A

- **Historically**
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