

Regulatory Challenges, Up dated Standards for Biological Evaluation and Specificities in Process Validation for Medical Devices in Dentistry

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1. Introduction:

The dental sector is a diverse and rapidly growing part of the medical device industry. Products range from basic instruments to implant systems, digital dentistry tools, abutments, cements, filling material, orthodontic systems, bone substitutes, 3D-printed restorations, etc, covering all MDR classification categories.

The regulatory landscape for dental medical devices has become increasingly demanding under the European MDR. Manufacturers face growing complexity due to borderline classifications and an exceptionally diverse product range.

The updated ISO 7405 and ISO 10993-1 standards (2025) further raise the bar on biological evaluation. These revisions introduce more stringent requirements for biocompatibility and long-term performance, especially for dental materials.

Process validation ensures that manufacturing steps continuously produce devices meeting predetermined specifications. This is crucial in dentistry, where product consistency directly affects clinical performance.

2. Regulatory Challenges Under MDR 2017/745:

2.1 MDR Classification

Medical Devices in Dentistry can fall into **Classes I, IIa, IIb or III** depending on factors such as:

- The duration and nature of tissue contact
- Whether the product is implantable
- Whether software influences diagnosis or treatment
- Whether the device is custom-made or mass-produced

Under MDR, **many dental devices fall into borderline categories** due to their varied risk profiles and clinical

applications. Misclassification remains one of the main reasons for delays during conformity assessment.

2.2 Risk Management

Risk Management according to **ISO 14971** is the fundamental element for demonstrating safety and performance. Tailored risk management files ensure full traceability between design, clinical data, usability outcomes and post-market-surveillance feedback.

2.3 Usability

Usability engineering according to **IEC 62366** is a critical requirement for dental products used in highly technical environments such as implants, and accessories designed for skilled professionals.

2.4 Clinical Evaluation: High Expectations for Safety and Performance

Dental implants, orthodontic appliances and digital dentistry systems require **solid clinical evidence** that demonstrates long-term performance.

Challenges include:

- Demonstrating equivalence (often rejected by Notified Bodies)
- Structuring clinical literature reviews
- Determining when a clinical investigation is unavoidable
- Addressing long-term follow-up expectations.

Manufacturers must balance **scientific robustness** with **pragmatic approaches** that remain feasible within SME budgets.

2.5 Post-Market Surveillance (PMS) and Post Market Clinical Follow up (PMCF)

Comprehensive PMS/PMCF-activities have to be performed to monitor on-going safety and field performance. For dental device manufacturers, the following plans have to be developed and results collected in reports:

- **PMS Plans and PSUR (Periodic Safety Update Report)** aligned with MDR requirements, MDCG 2025-10 and MDCG 2022- 21
- **PMCF Plans and PMCF Reports** aligned with MDR requirements, MDCG 2020-7 and MDCG 2020-8

2.6 Digital Dentistry and 3D Printing: A Rapidly Evolving Regulatory Landscape

Software used for diagnosis, treatment planning, imaging or CAD/CAM falls under **MDR rules for medical device software**.

Regulatory challenges include:

- Determining the correct classification under **Rule 11**
- **Cybersecurity** and data management expectations
- Validation of **3D-printed** custom devices
- Ensuring **consistency** between **design files, production steps** and **final output**

The intersection of software, materials and manufacturing creates a multidisciplinary regulatory burden for dental innovators.

3. Updates of ISO 7405 and ISO 10993-1 in 2025! Is your biological evaluation still up to date?

Both ISO 7405 and ISO 10993-1 were updated in 2025. While additional biocompatibility testing is not necessarily required, it is essential to ensure that your biological evaluation remains aligned with state-of-the-art standards, as biological evaluation is a continuous process throughout the medical device's lifecycle.

3.1 Update of ISO 10993-1:2025

Categorisation helps select appropriate biological effects to be evaluated based on the medical device clinical use. Following update of ISO 10993-1 in 2025, your categorisation may have changed! Here after some new considerations:

Potential reasonably foreseeable misuse, that may alter:

- Exposure duration
- Contact site (tissue/body)
- Target population
- Exposure duration calculations: referring now to “contact days” (regardless of actual usage time within that day)

Accordingly, you should **reevaluate your medical device categorisation**: are there some new biological effects (previously referred to as “biological endpoints”) to be addressed?

In addition, the new ISO 10993-1:2025 explicitly requires considering the severity and probability of potential biological harms when using a medical device: the so-called **biological risk estimation**. This step, essential for a fully compliant biocompatibility evaluation, is integrated into every Biological Evaluation Plan (BEP).

3.2 Update of ISO 7405:2025

ISO 7405 provides test methods for assessing the biological effects of dental medical devices that contact the patient and requires specific evaluations beyond the ISO 10993 series, depending on the medical device categorisation.

- Harmonised criteria for the **agar diffusion test** (aligned with ISO 10993-5)
- A new informative annex recommending the **Antioxidant Response Element (ARE) reporter assay** for detecting oxidative stress
- An additional informative annex supporting **stepwise toxicological assessment** and Margin of Safety (MoS) calculations in line with ISO 10993-17:2023

3.3 Recommended procedure

While these additions represent the current state-of-the-art, re-evaluation is not mandatory but ensuring compliance with the updated requirements is essential.

- **New medical device**: develop a **biological evaluation** in alignment with your risk management according to new ISO 10993-1 and ISO 7405 versions
- **Legacy medical devices** (medical devices already on the market): review your documentation and conduct a **gap analysis** of the current biological evaluation to ensure alignment with new ISO 10993-1 and ISO 7405
- In case of **gaps** evidenced (biological effects that are not covered, risk obtained from clinical field): **rationale/testing** to close the gaps!
- Medical device **change**: perform a **change assessment** to confirm continued compliance with the updated ISO 10993-1 and ISO 7405 requirements or perform new testing to align

3.4 Specific considerations for testing of medical devices used in dentistry

It is essential to clearly define and justify the **preparation of test samples** in order for the study results to be accepted by Notified Bodies. To do so, Instructions For Use

(IFU) should be followed as closely as possible along with recommendations of ISO 10993-12:2021 and ISO 7405:2025.

- If your medical device is **substance-based**: the impact of the substances (e.g., chlorhexidine) on the test results should be considered in the biological evaluation to avoid bias during testing procedures
- If your medical device is **degradable** and/or **absorbable**: special testing conditions may be applied. In addition, degradation has to be examined, including systemic effects of the degradation products. Toxicological evaluation of the degradation products and their toxicokinetic (i.e., ADME profile) should exclude a risk for the patient.

In case of **wear debris** the amount of debris during clinical use should be determined and a toxicological assessment evaluates the potential risk of the patient.

3.5 U.S. FDA requirements and chemical characterisation

ISO 7405 is recognized by the U.S. FDA as a consensus standard. Think about the Q-submission process to obtain U.S. FDA feedback on study designs before starting testing, which helps to save time, money and animal lives! The U.S. FDA also released a draft guidance on **Chemical Characterisation (CC)** in 2024, emphasizing CC as a key element in the biological evaluation of medical devices and a potential basis for waiving certain animal studies. CC should follow ISO 10993-18:2020/Amd 1:2022 requirements, with the subsequent **Toxicological Risk Assessment (TRA)** conducted according to **ISO 10993-17** and **supported by the new Annex E of ISO 7405:2025**.

4. Validation of Cleaning Processes, Reprocessing Procedures and Packaging as Central Topics for Medical Devices used in Dentistry!

Dental implants often require a final cleaning step at the end of their manufacturing process before packaging and sterilization.

Dental instruments are typically reprocessed using manual and/or automated cleaning and disinfection,

followed by sterilization.

Due to the wide variety of dental products, packaging must be selected carefully, and the packaging process must be validated. In addition, packaging stability and integrity must be demonstrated for the entire medical device intended shelf life.

4.1 Cleaning Validation of Medical Devices used in Dentistry

In recent years, cleaning steps for components and final products (e.g., dental implants) have increasingly been integrated into manufacturing process. These procedures range **from simple wiping to multistage cleaning baths and ultrasonication**. At the same time, **requirements for demonstrating cleaning efficacy have risen significantly**. Standards **deriving from ISO 19227**, prepared for cleaning validation of orthopedic devices, have been developed for other medical devices, such as **ASTM F3127**, **DIN/TS 5343** and **ISO/AWI 8250** (under preparation), and provide guidance on process design and validation.

However, a tailored approach is essential and often challenging. **Test methods must be selected** based on a risk analysis that considers potential contamination coming from materials, manufacturing steps, and considering the intended use of the medical device. **Equipment must be qualified, sample sizes defined, and acceptance criteria established**. Effective planning is crucial!

4.2 Reprocessing of Dental Instruments

For application of dental products like implants, fillers, abutments etc. suitable instruments are necessary and often reprocessed.

The following steps are necessary for reusables:

- **Risk analysis** and **classification (Spaulding)**, the grade and areas of contamination (e.g., bone, blood, saliva, tissue) on the medical device
- Determine level of **cleaning, disinfection and sterilization** (= reprocessing procedure)
- **Describe reprocessing procedure** in detail (see ISO 17664-1, ISO 17664-2 and U.S. FDA guidance) in the IFU (Instructions For Use)
- **Validate** at least one reprocessing procedure

Recently published ISO/DTS 17664-3 determines cleaning classification categories and designation of product families to cleaning processes which reduces effort and costs for validation studies when using a master product.

When planning test methods, different requirements for U.S. FDA or Europe must be considered, e.g., ANSI/AAMI ST98 versus ISO 15883-5 for cleaning validation, different microorganisms and acceptance criteria for disinfection validation (EN 14561, EN 14562 versus FDA guidance document, AAMI TIR12).

For moist heat sterilization, **instrument trays** may be used and representative products in the tray have to be chosen for validation.

But the most challenging part is the **lifetime evaluation**, which means performing the maximum number of reprocessing cycles or providing an end-of-life indicator. Several options are possible depending on the risk of the dental reusable product.

4.3 Packaging and Shelf Life Assessment of Medical Devices used in Dentistry

A wide range of packaging solutions—such as **implant holders, containers, syringes, pouches, and blisters**—is available for dental products. All packaging materials must comply with **ISO 11607-1**, and the packaging processes must be validated in accordance with **ISO 11607-2**, with additional guidance provided by ISO/TS 16775.

Packaging validation studies should be selected based on the packaging type and the target regulatory market. In addition, a **shelf life** must be established and declared on product packaging. As part of the assessment, the **integrity of the sterile barrier system, performance** of the medical device and biological safety aspects after aging, are important to be evaluated. Due to the high variability in the world of packaging solutions for dental medical devices, the strategy might significantly differ and individual strategy generation and further assessment is necessary.

Especially for new medical devices, for which **real-time**

aged samples are not yet available, approaches of **accelerated ageing** mimicking the assumed real-time ageing of the medical device, including interim investigations, could facilitate the evaluation process. This can facilitate the generation of preliminary results for an early adjustment of protocols whenever necessary.

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