Brief Report

Viable Biological Materials or Organisms in Regulation (EU) 2017/745 on Medical Devices

Javier Morán * and Alina Kilasoniya

Posted Date: 9 July 2024

doi: 10.20944/preprints202407.0761.v1

Keywords: viable biological materials; Regulation (EU) 2017/745; medical devices; microorganism inviability; regulatory compliance

Brief Report

Viable Biological Materials or Organisms in Regulation (EU) 2017/745 on Medical Devices

Javier Morán [1,*] and Alina Kilasoniya [2]

[1] Department of Food Innovation, Universidad Católica San Antonio de Murcia, 30107 Murcia, Spain
[2] International PhD School, Universidad Católica San Antonio de Murcia, 30107 Murcia, Spain
* Correspondence: jmoran@sat.ucam.edu

Abstract: Regulation (EU) 2017/745, addresses medical devices and clarifies the scope regarding products containing viable biological materials or organisms. This regulation excludes products containing viable cells or tissues of human or animal origin, as well as those containing viable biological materials or organisms of other origins intended to achieve or support the intended purpose of the products. The term "inviable" is defined as incapable of metabolism or multiplication. The regulation mandates that products manufactured using non-viable biological substances must ensure the highest safety standards, including validated methods of elimination or inactivation of transmissible agents during manufacturing. Several Directives and Regulations provide context for the term "viable" in medical devices, emphasizing the device's ability to perform effectively and safely. Notified Bodies in the EU have interpreted that thermally inactivated microorganisms in a product do not classify it as a medical device under Regulation 2017/745. To address this, it is crucial to differentiate between the inactivation of microorganisms and the viability of their metabolites. Demonstrating the inviability of microorganisms through rigorous testing and evidence is essential for regulatory compliance and safe use in medical products. Clarifying these points and providing necessary evidence can establish that inactivated microorganisms are inviable and meet the requirements for use in medical products.

Keywords: viable biological materials, Regulation (EU) 2017/745, medical devices, microorganism inviability, regulatory compliance

1. Introduction

Regulation (EU) 2017/745 of the European Parliament and of the Council, dated 5 April 2017, addresses medical devices and amends Directives 2001/83/EC, Regulation (EC) No 178/2002, and Regulation (EC) No 1223/2009, while also repealing Council Directives 90/385/EEC and 93/42/EEC. A crucial aspect of this Regulation is the clarification regarding products containing viable biological materials or organisms (Regulation (EU) 2017/745).

2. Regulation (EU) 2017/745

Regulation (EU) 2017/745 in its recital (13) states that "it should be clarified that, just as products containing viable cells or tissues of human or animal origin are explicitly excluded from Directives 90/385/EEC and 93/42/EEC and, therefore, from this Regulation, products containing or consisting of viable biological materials or viable organisms of other origins intended to achieve or support the intended purpose of those products are also not regulated by this Regulation."

Moreover, in Chapter I, Scope and Definitions, Article 1, Objective and Scope, point 6 specifies that "this Regulation shall not apply to: (h) products, other than those referred to in points (d), (f), and (g), that contain or consist of viable biological material or viable organisms, including living microorganisms, bacteria, fungi, or viruses, intended to achieve or support the intended purpose of the product."

In Article 2, Definitions, it is specified that for the purposes of this Regulation, "16) 'inviable' means incapable of metabolism or multiplication."

 doi:10.20944/preprints202407.0761.v1

Finally, Annex I, 13. Products Incorporating Materials of Biological Origin, states in section 13.3 that "with regard to products manufactured using non-viable biological substances other than those referred to in sections 13.1 and 13.2, the processing, preservation, evaluation, and handling of such substances shall be carried out in a way that offers the highest guarantees of safety for patients, users, and, where applicable, other persons, including in the waste disposal chain. Specifically, to offer guarantees that they are free of viruses and other transmissible agents, appropriate sourcing methods shall be used and validated methods of elimination or inactivation applied during the manufacturing process."

In summary, the Regulation does not apply to products containing or consisting of viable biological material or viable organisms; it defines "inviable" as the inability to undergo metabolism or multiplication; and advocates the use of appropriate and validated inactivation methods during the manufacturing process.

3. Definitions of "Viable" in Previous Directives and Regulations

3.1 Directive 90/385/EEC: The viability refers to the ability of an active implantable medical device to function effectively and safely in the human body after implantation, performing its intended functions according to the manufacturer's specifications without causing harm to the patient (Council Directive 90/385/EEC).

3.2 Directive 93/42/EEC: The viability relates to the ability of a medical device to perform its intended function effectively and safely in the clinical environment for which it was designed, without causing harm to the patient or user (Council Directive 93/42/EEC).

3.3 Directive 2004/23/EC: The viability refers to the ability of human cells and tissues to maintain their functionality, structural integrity, and ability to perform biological functions after being processed and stored for use in transplants. These requirements aim to ensure that human cell and tissue products meet the necessary quality and safety standards for transplant use and minimize the risk of adverse effects for recipients (Directive 2004/23/EC).

3.4 Regulation 1394/2007: The viability implies the ability of living cells or tissues to maintain their function and biological activity after being processed and prepared as advanced therapy medicinal products, meeting the quality, safety, and efficacy standards established in the Regulation, as well as additional requirements applicable to advanced therapy medicinal products (Regulation (EC) No 1394/2007).

3.5 Regulation 2017/745: Although the term "viable" is not explicitly used in the MDR to define medical devices, within the context of the Regulation, the "viability" of a medical device can be understood in terms of its ability to meet the essential safety and performance requirements established in the MDR. Under the MDR, a medical device is considered "viable" when it meets the criteria for safety, efficacy, and quality established in the Regulation. This implies that the device must be manufactured according to applicable quality standards, demonstrate clinical efficacy, and be safe for its intended use according to the risk assessment conducted by the manufacturer.

3. Practical Considerations

A Notified Body is an organization designated by an EU Member State (or by other countries under specific agreements) to assess the conformity of certain products before they are placed on the market. These bodies are authorized to carry out tasks related to conformity assessment procedures established in the applicable legislation where third-party intervention is required (European Commission. "Medical Devices: Notified Bodies.").

Several Notified Bodies for Medical Devices in the European Union have issued responses that seem to link product viability with a particular interpretation of the term "viable." Specifically, they have highlighted that the presence of thermally inactivated probiotics in a medical device does not allow the product to be classified as a medical device as indicated in Regulation 2017/745 Article 1 Chapter 6 - point h, assuming that these microorganisms should be considered viable.

According to Regulation 2017/745, "inviable" means "incapable of metabolism or multiplication," implying that "inviable" refers to the inability of an organism or biological material to carry out

 doi:10.20944/preprints202407.0761.v1

metabolic processes or reproduce. In other words, an organism or biological material would be considered "inviable" if it cannot maintain its normal biological function, such as cellular metabolism or cell multiplication. In the context of biology, an inviable organism cannot survive or function properly in its natural environment due to some genetic defect, cellular damage, adverse environmental conditions, or other factors that impede its normal living capacity (Allison 1999).

To avoid a basic conceptual error, we must differentiate between the microorganism used and the metabolites it produces after inactivation and especially not confuse inviability with inactivation (Morán and Kilasoniya 2024). Thus, thermally inactivated probiotics would be inviable, but their metabolites would not. The microorganism, being inviable, would not have the capacity for metabolism or multiplication by itself, thus complying with the terminological definition of "inviable" as stated in Regulation 2017/745 and therefore could be registered as a medical product (Weigel et al. 2017).

The microorganism exposed to extreme conditions, such as high temperatures, can no longer perform its normal metabolic functions and would thus be considered inviable. In summary, "inviable" would mean that the microorganism (not its metabolites) lacks the capacity for metabolism or multiplication, resulting in its inability to survive or function normally in a biological environment (Olteanu et al. 2024).

A non-viable cell can maintain some metabolic activity for a brief period after death, a phenomenon known as post-mortem metabolism. However, it is important to note that this activity is limited and eventually ceases as the cell components degrade (Galluzzi et al. 2018).

To determine if a microorganism is inactive or inviable, it is essential to consider several factors and considerations that any regulator will request (Greening, Grinter, and Chiri 2019; Sagripanti et al. 2011; Meyer et al. 2023; Maftei et al. 2024; Mosca et al. 2022):

1. Definition of Inactivity or Inviability: In the context of thermally inactivated probiotics, it is crucial to clearly define what is meant by "inactive" or "inviable" in terms of microorganisms, as explained before. We must be able to demonstrate that after inactivation there is a loss of cellular viability, that is, the microorganisms are incapable of growing, reproducing, or performing vital metabolic functions.

2. Inactivation Methods: It is important to specify the methods used to inactivate the microorganism. It is necessary to demonstrate that the inactivation process used is effective and has resulted in the total loss of cellular viability.

3. Viability Tests: To support the claim that the inactive microorganism is inviable, specific viability tests will be required. These tests can include viable cell counts, microbial growth analysis, cell viability tests, etc.

4. Scientific Evidence: We must provide solid scientific evidence and data to demonstrate that the microorganism is inactive and inviable after the thermal inactivation process. This can include stability studies, microbiological analyses, process validation data, etc.

If we can clarify all these points, we can demonstrate that the inactivated microorganism is inviable and, therefore, falls within the components that can be used in medical products.

4. Conclusions

The aforementioned responses received regarding the viability of the product seem to be linked to a particular interpretation of the term "viable," and according to the interpretation of the regulation made by certain Notified Bodies, the presence of thermally inactivated microorganisms in the product does not allow it to be classified as a medical device according to Regulation 2017/745.

To address this situation, it is important to correctly understand the definition of "inviable" according to the regulation. In this context, "inviable" refers to the inability of an organism or biological material to carry out metabolic processes or reproduce. Therefore, an organism would be considered "inviable" if it cannot maintain its normal biological function due to adverse conditions or cellular damage. It is crucial to differentiate between the inactivation of the microorganism and the viability of its metabolites. The thermally inactivated microorganism is inviable, but its metabolites remain functional (Vinderola et al. 2022).

Therefore, to determine the viability of the microorganism, it is necessary to clearly define the terms "inactive" and "inviable" and provide solid evidence supporting this claim. Several factors, such as the inactivation methods used, viability tests, and scientific evidence, must be considered to demonstrate that the inactive microorganism is inviable and, therefore, can be considered safe for use in medical products. If these points can be clarified and the necessary evidence provided, it is possible to demonstrate that the inactivated microorganism is inviable and meets the requirements for use in medical products (Prajapati et al. 2023; Ma, Tu, and Chen 2023).

Thus, the viability of biological materials in medical devices is a critical aspect regulated under Regulation (EU) 2017/745. Understanding and demonstrating the inviability of microorganisms through rigorous testing and evidence is essential for compliance and safe use in medical products. Clarifying these points and providing the necessary evidence can demonstrate that the inactivated microorganism is inviable and meets the requirements for use in medical products.

6. Patents

There are no patents resulting from this work.

Author Contributions: Conceptualization, J.M.; methodology, J.M..; software, A.K.; validation, J.M., and A.K..; formal analysis, J.M.; investigation, J.M. and A.K.; resources, J.M.; data curation, J.M.; writing—original draft preparation, J.M. and A.K.; writing—review and editing, J.M. and A.K.; visualization, A.K..; supervision, J.M.; project administration, A.K.; funding acquisition, A.K.. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Food Consulting & Associates.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References

1. (Allison 1999) Allison, D.G. "A Review: Taking the Sterile Out of Sterility." Journal of Applied Microbiology 87, no. 6 (1999): 789-93. doi:10.1046/j.1365-2672.1999.00948.x.
2. (Council Directive 90/385/EEC) Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.
3. (Council Directive 93/42/EEC) Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
4. (Directive 2004/23/EC) Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.
5. (Galluzzi et al. 2018) Galluzzi, L., I. Vitale, S. Aaronson, et al. "Molecular Mechanisms of Cell Death: Recommendations of the Nomenclature Committee on Cell Death 2018." Cell Death & Differentiation 25 (2018): 486–541. https://doi.org/10.1038/s41418-017-0012-4.
6. (Greening, Grinter, and Chiri 2019) Greening, C., R. Grinter, and E. Chiri. "Uncovering the Metabolic Strategies of the Dormant Microbial Majority: Towards Integrative Approaches." mSystems 4 (2019). doi:10.1128/msystems.00107-19. https://doi.org/10.1128/msystems.00107-19.
7. (Maftei et al. 2024) Maftei, Nicoleta-Maricica, Cosmin Raducu Raileanu, Alexia Anastasia Balta, Lenuta Ambrose, Monica Boev, Denisa Batîr Marin, and Elena Lacramioara Lisa. "The Potential Impact of Probiotics on Human Health: An Update on Their Health-Promoting Properties." Microorganisms 12, no. 2 (2024): 234. https://doi.org/10.3390/microorganisms12020234.
8. (Ma, Tu, and Chen 2023) Ma, L., H. Tu, and T. Chen. "Postbiotics in Human Health: A Narrative Review." Nutrients 15, no. 2 (2023): 291. doi:10.3390/nu15020291.
9. (Meyer et al. 2023) Meyer, C.T., G.K. Lynch, D.F. Stamo, E.J. Miller, A. Chatterjee, and J.M. Kralj. "High Throughput Viability Assay for Microbiology." bioRxiv [Preprint] (2023). doi:10.1101/2023.01.04.522767. Update in: Nature Microbiology 8, no. 12 (2023): 2304-2314. doi:10.1038/s41564-023-01513-9.
10. (Morán and Kilasoniya 2024) Morán, Javier, and Alina Kilasoniya. 2024. "Integration of Postbiotics in Food Products through Attenuated Probiotics: A Case Study with Lactic Acid Bacteria in Bread." Foods 13, no. 13: 2042. https://doi.org/10.3390/foods13132042.
11. (Mosca et al. 2022) Mosca, A., Y. Abreu, A.T. Abreu, K.A. Gwee, G. Ianiro, J. Tack, T.V.H. Nguyen, and C. Hill. "The Clinical Evidence for Postbiotics as Microbial Therapeutics." Gut Microbes 14, no. 1 (2022). doi:10.1080/19490976.2022.2117508.

12. (Olteanu et al. 2024) Olteanu, Gabriel, Maria-Alexandra Ciucă-Pană, Ștefan Sebastian Busnatu, Dumitru Lupuliasa, Sorinel Marius Neacșu, Magdalena Mititelu, Adina Magdalena Musuc, Corina-Bianca Ioniță-Mîndrican, and Steluța Constanța Boroghină. "Unraveling the Microbiome–Human Body Axis: A Comprehensive Examination of Therapeutic Strategies, Interactions and Implications." International Journal of Molecular Sciences 25, no. 10 (2024): 5561. https://doi.org/10.3390/ijms25105561.
13. (Prajapati et al. 2023) Prajapati, N., J. Patel, S. Singh, V.K. Yadav, C. Joshi, A. Patani, D. Prajapati, D.K. Sahoo, and A. Patel. "Postbiotic Production: Harnessing the Power of Microbial Metabolites for Health Applications." Frontiers in Microbiology 14 (2023). doi:10.3389/fmicb.2023.1306192.
14. (Regulation (EC) No 1394/2007) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.
15. (Regulation (EU) 2017/745) Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
16. (Sagripanti et al. 2011) Sagripanti, J.L., B. Hülseweh, G. Grote, L. Voss, K. Böhling, and H.J. Marschall. "Microbial Inactivation for Safe and Rapid Diagnostics of Infectious Samples." Applied and Environmental Microbiology 77, no. 20 (2011): 7289-95. doi:10.1128/AEM.05553-11.
17. (Vinderola et al. 2022) Vinderola, G., M.E. Sanders, S. Salminen, and H. Szajewska. "Postbiotics: The Concept and Their Use in Healthy Populations." Frontiers in Nutrition 9 (2022). doi:10.3389/fnut.2022.1002213.
18. (Weigel et al. 2017) Weigel, K.M., F.K. Nguyen, M.R. Kearney, J.S. Meschke, and G.A. Cangelosi. "Molecular Viability Testing of UV-Inactivated Bacteria." Applied and Environmental Microbiology 83, no. 10 (2017): e00331-17. doi:10.1128/AEM.00331-17.
19. (https://health.ec.europa.eu/medical-devices-topics-interest/notified-bodies_en) European Commission. "Medical Devices: Notified Bodies." Accessed July 3, 2024. https://health.ec.europa.eu/medical-devices-topics-interest/notified-bodies_en.