POTENTIAL STERILIZATION METHODS FOR IMPLANTABLE DEVICE FOR THERAPEUTIC DELIVERY

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INTRODUCTION

Surgical implants intended to deliver therapeutics should fulfill essential requirements, such as mechanical and chemical stability in physiological environment during treatment of a disease or during their lifespan, and then be explanted or gradually degraded. In order to guarantee proper functioning of such system, especially in the case of complex configuration or multifunctional tasks of the implant, e.g. active medical devices, besides selection of biomaterials and involved manufacturing processes, the designer should also consider potential sterilization method. Academia scientist involved in early stage development of a system delivering therapeutics often ignore possible detrimental effect of sterilization on material properties or functioning of the device. Though the sterilization by a validated method is critically needed when it comes to commercialization of the new device. Validation of selected sterilization technique in terms of its effectiveness, reliability and reproducibility is the prerequisite the manufacturer is requested to demonstrate to the notifying authorities in order to prove microbiological safety of the new device.

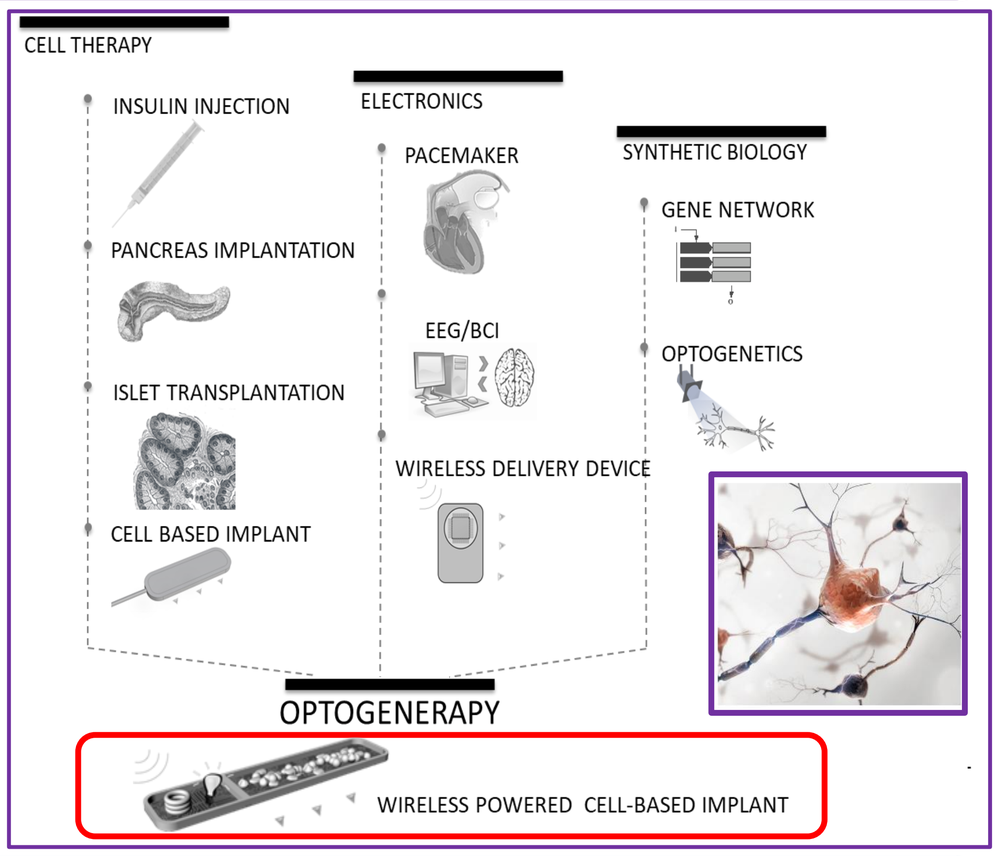
✓ **Multiple Sclerosis (MS)** is a potentially disabling disease of the Central Nervous System; ✓ **700.000** people have Mulitiple Sclerosis in Europe;
✓ Affects people most frequently between the **ages of 20 and 40**; ✓ 70% are diagnosed during working years; ✓ About **2/3** of the people affected are women;
✓ More than 50% of the patients and their relatives suffer steep income loss within a few years; ✓ IFN-β therapies represent 45% of total MS therapies market;
✓ Up to 35% of MS patients using IFN-β are non-adherent; ✓ By 2010 the market revenue of MS therapies was **€ 2.3 billion** in Europe;

GOAL

Develop and validate a new optogenetic implant for controlled interferon beta (IFN-ß) protein delivery for treating patients with Multiple Sclerosis (MS) in order to **improve quality of life of MS patients** through ✓ eliminating short and long term effects of serial injections; ✓ increased therapeutic efficiency due to medication adherence.

The implant combines and develops complementary knowledge from various fields:

- **Polymeric biomaterials** with strong optical, biocompatibility and barrier requirements;
- **Optoelectronics** miniaturization, autonomy and optical performance;
- **Cellular engineering** design for stability and performance of the synthetic optogenetic gene pathway over long-term implantation;
- **Micro moulding** enabling embedding optoelectronics and other components.



MATERIALS

Optogenetic Implant, consisting of:

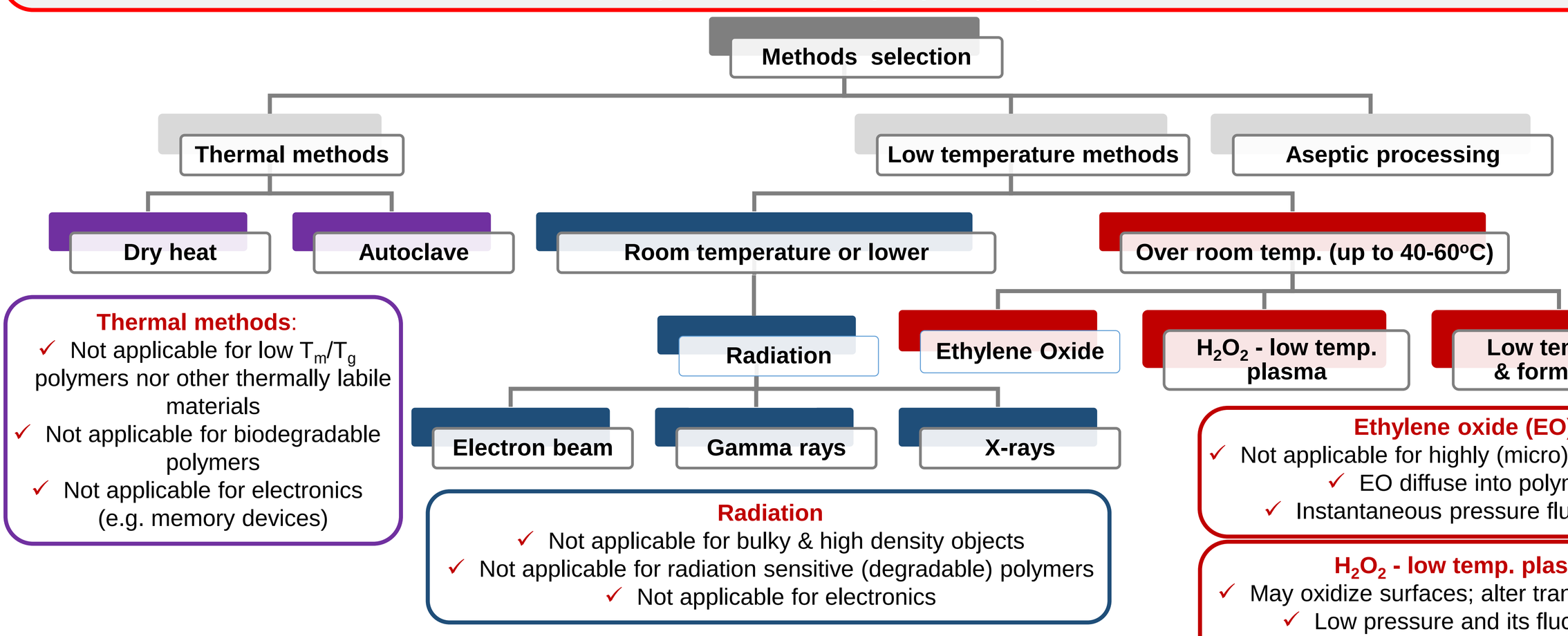
- Drug delivery **cell chamber**: composed of a frame of biocompatible optical polymer with the surfaces closed by flat membranes;
- **Optoelectronics module**: a micro-power energy harvesting antenna and rectifying circuit controlling a NIR-LED, packaged in a hermetic and stable material.

METHODS

The theoretical approach to selection of potentially applicable sterilization methods is based on the knowledge of properties of the polymeric materials composing the device of bio-electronic implant intended for delivering therapeutics from genetically engineered cells stimulated by light, the complexity of its design and presence of sensitive components or subsystems. The device should be provided sterile for cells loading, therefore terminal sterilization of manufactured implant or aseptic processing of pre-sterilized components may be applied.

DISCUSSIONS

The manufacturer intended to distribute medical products within EU should follow regulations specified in directives of **90/385/EEC, 93/42/EEC, 98/79/EC**, updated with Regulation **(EU) 2017/745** of April 5th 2017, with regards to sterilization, and further, may follow the guidance provided in ISO standards. Reduction of the bioburden on and in the device to **Sterility Assurance Level (SAL) 10^{-6}** is required.



Thermal methods:
✓ Not applicable for low T_m/T_g polymers nor other thermally labile materials
✓ Not applicable for biodegradable polymers
✓ Not applicable for electronics (e.g. memory devices)

Radiation
✓ Not applicable for bulky & high density objects
✓ Not applicable for radiation sensitive (degradable) polymers
✓ Not applicable for electronics

Ethylene oxide (EO)
✓ Not applicable for highly (micro)porous objects
✓ EO diffuse into polymer
✓ Instantaneous pressure fluctuations

H_2O_2 - low temp. plasma
✓ May oxidize surfaces; alter transparency, blur
✓ Low pressure and its fluctuations
✓ Not applicable for semiconductors

LTSF, Steam & formaldehyde:
✓ may react with surface
✓ polymers, rubber may be damaged

CONCLUSIONS

The course of selection of potentially applicable sterilization methods for developed implantable bioelectronic device for therapeutics delivery is presented. **Low temperatures methods of EO, H_2O_2 - plasma and LTSF are applicable**. Validation of these methods will be done experimentally, according to specific ISO guidances, evaluating possible alternation of physical and chemical properties of the implant, and followed by biocompatibility and functional assessment.

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