Phantoms for performance verification and quality control in developing a photonics-based medical device (VASCOVID): a regulatory driven approach

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Abstract: We propose a standardized approach for performance assessment and quality-control of the novel VASCOVID system based on optical phantoms. This approach is tailored to meet the requirements of the Medical Device Regulation, and is extendable to other biophotonics devices.

1. Introduction

Optical phantoms are critical for testing, validation, characterization and optimization of biophotonics technologies [1]. Numerous phantom recipes have been developed, basic optical phantoms are made of three key ingredients: a bulk medium (water, epoxy resin, silicone, or agar), absorber (India ink, printer toner, black silicone, or dye) and scatterer (intralipid, titanium oxide, aluminum oxide, or silica microspheres) [2]. Despite these advancements, there is a gap in the use of phantoms to address Regulation (EU) 2017/745 on Medical Devices (Medical Device Regulation, MDR) of biophotonics devices. A recent standardization initiative has given the first optical phantom driven standard for performance assessment of functional near infrared spectroscopy (fNIRS) device, however, this is limited in the scope to fNIRS devices [3]. There are ongoing initiatives at European and international level to create general phantom based standards for biophotonics device testing, verification and quality control, but the concensus of various stakeholders is still an ongoing process. Various literature and protocols have been developed to use phantoms as reliable tools to assess the performance of biophotonics devices. Nevertheless, there's a lack of dedicated literature on how these phantoms can be exploited for manufacturing quality control and lifetime surveillance, aspects that are considered critical under the MDR [4].

The Horizon 2020-funded European emergency project VASCOVID (https://vascovid.eu/) is developing a portable, cost-effective, non invasive and real time health monitoring platform for the stratification and management of microvascular health in severe COVID-19 patients at the intensive care (ICU), within 2 years starting from December 2020. The ambitious VASCOVID device combines state-of-the-art bio-photonics technologies, time-resolved near infrared spectroscopy (TR-NIRS) and diffuse correlation spectroscopy (DCS), alongside artificial intelligence (AI) to impact COVID-19 patients healthcare outcome. The VASCOVID platform will de designed and built employing international technical standards in order to meet the General Safety and Performance Requirements (GSPR) outlined in the MDR. The performance of the core technologies TR-NIRS/DCS are traditionally validated using phantoms. To enable the design and manufacture of VASCOVID as a MDR-compliant device, a well documented and quality controlled phantom manufacturing and characterization is essential. The final optical parameters (abosorption, scattering, blood flow index) of the phantom have to be verified against the best known reference standards estabilished in literature for TR-NIRS/DCS technologies.

In this work (see Fig. 1) , we present three types of phantoms to assess the performance and control the quality of VASCOVID devices across the value chain (components, development of modules, integration, prototyping, and surveillance during daily use during the device life time). In the VASCOVID case, there is a lack of an international standard for the use of phantoms for performance assessement. Therefore, we developed a protocol based on the state-of-the-art literature reference standard, based on intralipid phantoms (type 4 in Fig. 1) to quality control the

phantom manufacturing and characterization process. We will present the aforementioned methods and application to TR-NIRS and explore an extension to DCS.

2. Standardized approach

Fig. 1 shows the different types of phantoms proposed to address end-to-end quality control of VASCOVID device and manufacturing process. The different types of phantoms can be described as below.

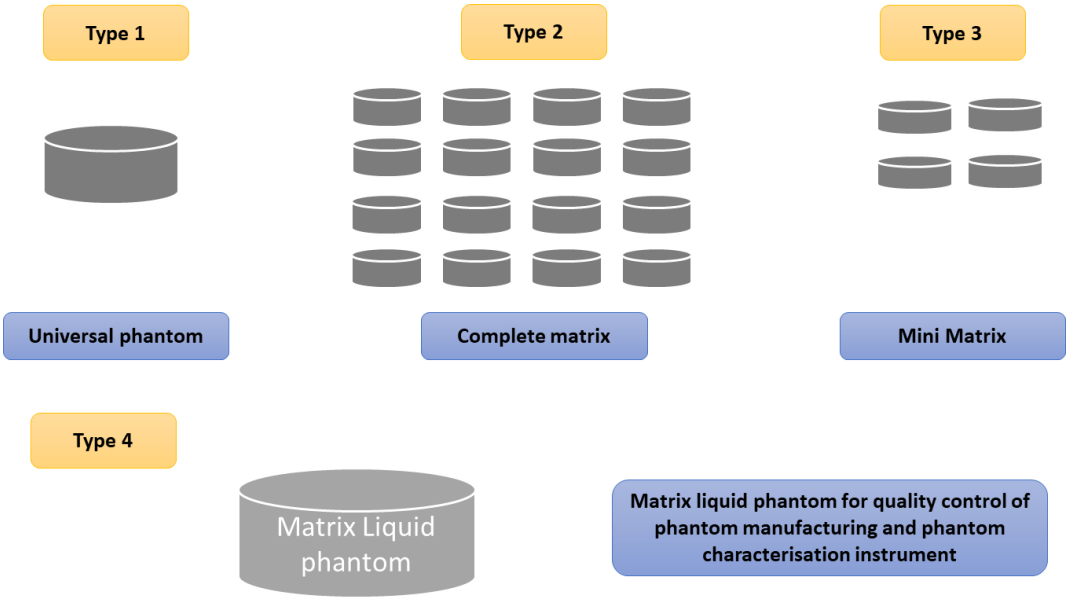

Fig. 1. Three types of solid phantoms (type 1-3) for end-to-end quality control of VASCOVID devices, from the manufacturing phase to day-to-day surveillance during the device life-time, and a type 4 liquid phantom for quality control of the phantoms themselves.

Types of phantoms

1) **Type1 – Universal phantom:** A single universal phantom will be produced to enable end user to assess performance in regular intervals (weekly, monthly) for the device validation. From a regulatory perspective, this will be considered as accessory (part of minimal viable product-MVP) to be sent along with the VASCOVID device. The critical parameter for the universal phantom will be the long term stability.
2) **Type2 – Matrix:** Complete MEDPHOT Matrix [5] range of 16 phantoms for quality control assessment of each VASCOVID modules and integrated device during manufacturing over entire optical properties range of interest (absorption μ_a: 0-.3 cm^{-1}, reduced scattering μ'_s: 5-20 cm^{-1}). The critical parameters to be considered are linearity and accuracy along with long term stability.
3) **Type3 – mini Matrix:** A subset of matrix phantoms (4 phantoms) which will be used by the manufacturer for the calibration check during the scheduled quality check of VASCOVID device at manufacturer site. The critical parameters for the mini matrix are linearity and accuracy along with long term stability.
4) **Type4 – (Liquid reference phantom)** Use of liquid phantoms as gold standard to quality control phantom manufacturing and characterization process. In this way, the rich literature in the use of liquid phantoms as reference standard can be extended to solid phantoms.

Quality control of Solid phantoms manufacturing and characterization by reference liquid (intralipid) phantoms

Intralipid phantoms can be considered as the best known state-of-the-art reference phantoms in literature [6]. The purpose of this Type4 phantom is to benchmark the solid phantoms and phantom characterization instrument performance with well established intralipid phantoms. We chose solid phantoms for VASCOVID as they are long lasting, robust, less cumbersome as compared to liquid phantoms. A novel protocol based on well established MEDPHOT will be exploited for this purpose. The performance of characterization tool and reliability of phantom manufacturing process will be evaluated through following assays as outlined in MEDPHOT protocol [5].

The absolute optical properties (absorption, scattering) will be assessed by measuring the well known water spectrum, in addition to titrated spectra of indian ink. Linearity: the linearity of the recipe and characterization tool will be assessed at VASCOVID device wavelengths (690, 785, 830 nm). The reproducibility of the solid phantoms will be compared with reference intralipid phantoms. The long term stability will be assessed over months as it plays a critical role for the universal phantom which will be part of MVP of VASCOVID.

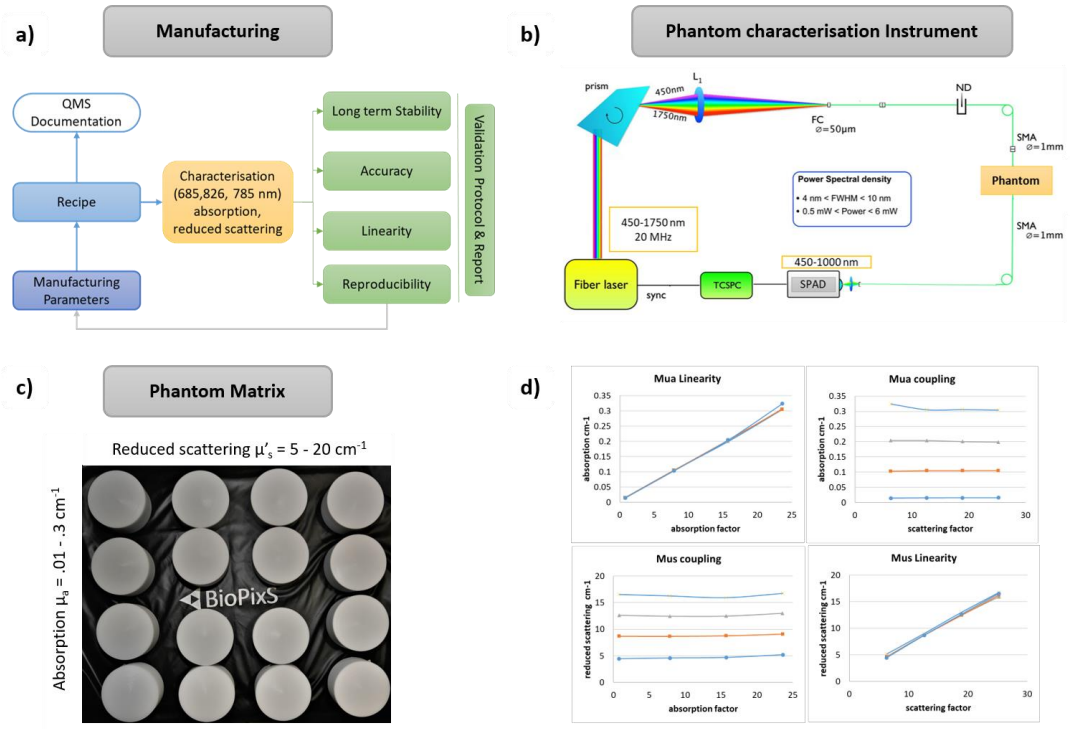

Fig.2 a) overviwe of phantom manufacturing, b)layout of phantom characterization instrument, c) sample BioPixS Matrix 16 phantoms for type 2 phantoms, d) linearity relation of Matrix 16 phantoms at 830 nm.

Fig. 2a illustrates the iterative manufacturing process to achieve well controlled manufacturing of phantoms [7]. The optical chain of time domain diffuse optical spectrometer which will be quality controlled by Type4 phantom is shown in Fig. 2b. Fig 2c and 2d shows the BioPixS Matrix 16 phantom kit and the linearity of the phantoms at 830 nm, respectively.

3. Conclusions

We propose a standardized approach based on 3 level phantoms for performance assessment, quality control during manufacturing and lifetime surveillance of VASCOVID devices. To the best of our knowledge this is the first of the kind of study to develop elaborate phantoms to assess performance and quality control of biophotonics medical device across the value chain (components, development of modules, integration, prototyping, surveillance during life time), and is tailored to meet requirements of MDR.

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References

[1] S. Konugolu Venkata Sekar et al, "Broadband Time Domain Diffuse Optical Reflectance Spectroscopy: A Review of Systems, Methods, and Applications." Appl. Sci., 9, 5465 (2019).
[2] B. W. Pogue et al., "Review of tissue simulating phantoms for optical spectroscopy, imaging," J. Biomed. Opt. 11(4), 041102 (2006).
[3] IEC 80601-2-71:2015 - Medical electrical equipment - Part 2-71: Particular requirements for the basic safety and essential performance of functional near-infrared spectroscopy (NIRS) equipment
[4] https://ec.europa.eu/health/md_sector/overview_en
[5] A. Pifferi, et al. "Performance assessment of photon migration instruments: the MEDPHOT protocol.," Appl. Opt., 44(11), 2104–2114 (2005).
[6] L. Spinelli et al., "Determination of reference values for optical properties of liquid phantoms based on Intralipid and India ink," Biomed. Opt. Express 5, 2037-2053 (2014)
[7] S. Konugolu Venkata Sekar *et al.*, "Solid phantom recipe for diffuse optics in biophotonics applications : a step towards anatomically correct 3D tissue phantoms," Biomed Opt Exp vol. 10, no. 4, pp. 2090–2100, 2019.