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Applying S.P.E.L. standard to patient matched devices: The need for a transparent regulatory matrix to qualify new manufacturing methods and technologies.

Applying S.P.E.L. (safety and performance evidence level) standard to patient matched medical devices: The need for a transparent regulatory matrix to qualify new manufacturing methods and technologies

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Introduction. In the field of personalized medicine, in connection with "smart implants" and in the interaction of various industries, new solutions are constantly being researched to give implant materials special properties and enhanced characteristics. On several levels and multiple medtech market segments, there is a need for implant materials and manufacturing methods that match ideally the patient's needs, fit and heal optimally within the patient's anatomy and remaining stable anchored as well as free of any adverse effects.

To provide implants, implant materials and geometries with such improved mechanical or biological properties, the industry offers a wide variety of solution methods, ranging from coating processes to novel composite materials[1] on the material side and new manufacturing methods such as additive manufacturing including 3D-printing, which may offer completely new possibilities[2].

But often research projects and innovative industrial applications have one thing in common: a lack of transparent, cross-industry and generally valid systems and procedures for objective quality evaluations but also safety and performance characteristics, of these individual developed and manufactured devices.

Keywords: patient matched implant, patient specific, 3D print, additive manufacturing, safety, performance, S.P.E.L., MDR, regulation, point of care.

Opinion. New manufacturing methods that promise unimagined freedom in design and development, but also in production and distribution, often inspire bold ideas: Provision of implants on demand, production of patient-specific implants directly in the operation room, combination of artificial and biological materials, tissue printing up to the printing of whole organs[3,4]. It is important to have these visions in mind: This is the only way to free implant manufacturing from traditional process constraints. Often, production, working-principles and applications of implants still reminds us of the previous century. There are industries that are already using the Industry 4.0 concept and the use of artificial intelligence far more creatively than medical technology. Medical technology has long been considered a rather cumbersome industry, and interdisciplinary thinking is often still in its infancy.

However, medical technology often seems cumbersome for one reason in particular, and that is due to the fact that medical devices have to undergo established and fixed procedures for verification, validation and approval combined with legal restrictions and insurance issues.

However, regulations and legal texts such as standards and norms and/or the Medical Device Regulation (Regulation EU 2017/745) are not written to anticipate safety and performance requirements for future technologies but attempt to describe what is already established in a set of regulations. Innovative technologies are therefore not found in these texts and fall outside the scope.

To ensure that innovative technologies can still be used in the treatment of patients, it is particularly most important to know exactly the applicable standards and laws. Only in this way it can be ensured that the "spirit" of the underlying regulation is adhered to, even in the case of new, innovative and promising technologies, and that the requirements of the regulations and laws are also adapted and applied in their “original sense” to new technologies and methods.

The lowest common, but most important denominator must be found here and can be described as follows: *to ensure the safety and performance of medical technology at all times by means of a transparent and risk-based approach*.

Abbreviation	Definition
3DPT	3D Printing Technology (3DPT): Additive manufacturing method.
4C	Strategic regulatory approach, defined and described as regulatory thinking, respecting the four Cs (4C) in medical technology: Commercialization, Certification, Clinical Evaluation, Copyright.
EBM	Electronic Beam Melting
FFF	Fused Filament Fabrication
MDR	Medical Device Regulation (MDR) provides the legal framework (EU) and stipulates mandatory requirements on how to plan, develop, manufacture, and market medical devices.
SIM	Standard Implantable Material, such as Titanium and/or Polymers, Ceramics
SLM	Selective Laser Melting
SLS	Selective Laser Sintering
SPEL	Safety and Performance Evidence Level (SPEL): Scoring system indicating the evidence level for evaluating the safety and performance requirements of 3DPTs in %.
SPR	Safety and Performance Requirements (SPR): Requirements that every medical product has to fulfill, according to the scope they belong to. These essential requirements are described by the Medical Device Regulation (EU) 2017/745 in Annex 1.

Table 1: Terms and definitions

This should be the common thread to follow. Often, this approach slows things down considerably and clips the wings of some overly inspired ideas: But in the interest of patient safety, this principle shall always be followed.
The focus here should not be on stubbornly following rules that have already been laid down, but it should be replaced by the concept of regulatory thinking in design, development and production. Regulatory thinking describes a strategic regulatory approach developed by the authors together with the 4C accelerator operated by the Medical Innovation Incubator and the Foundation for Medical Innovation, Tübingen as a regulatory strategy that knows existing rules, regulations, standards and norms, adapts them to new challenges and applies them in the spirit of the "original idea". Perspective. In a joint scientific positioning paper and currently restricted to surface functionalization technologies, experts from industry, research, clinics and regulatory affairs are now calling for uniform evaluation procedures and, with S.P.E.L., have created such a system: An evaluation matrix that makes it easy and objectively understandable for decision-makers and economic players in the healthcare system to assess the quality standard of surface functionalizations[5].

With the current paper the authors describe the possibility and need to adapt such a system like S.P.E.L. to all technologies and methods where no harmonized standards are in place and existing regulation don't exactly match, allowing for a comparable and transparent quality assessment. Medical Devices [MDs], In-Vitro Diagnostics [IVDs] or Personal Protective Equipment [PPE] products are CE marked to show that the products meet essential safety, health and performance requirements, that the legal manufacturer has performed tests and analyses explicitly prescribed by the various EU-regulations[6,7,8], and has established, maintains and operates a coherent quality management system: The CE mark confirms the safety and performance of the product on the one hand and on the other hand it distinguishes the manufacturer and certifies that he runs all company processes in accordance with the applicable standards, regulations, directives and laws, which are prescribed to respect.

In some areas, however, especially with new technologies and applications, there are no common standards or regulations, but rather more standards derived from the manufacturer's know-how. In other areas or in exceptional and emergency cases, such as COVID-19 / Corona- SARS-CoV-2 pandemic, for example, it is crucial to act fast and firm. In such an emergency situation a manufacturer cannot comply nor first perform all the prescribed formal test routines, lasting for months. In these serious situations, the manufacturer must carry out quality assurance and must develop and market his products in such a way that safety and performance is guaranteed if the product is used within its intended use.

To certify a sustained commitment to qualitatively high-standing product standards and an implemented quality management system of the manufacturer S.P.E.L. was developed and set effective by the authors.

Implant materials that are approved for their use in humans can be roughly divided into three material categories: Metals, ceramics, and polymers. The first attempts to use metals in implantology were related to the reconstruction of fractures of the long bones and their joints. The British surgeon Sir William Arbuthnot Lane (1856-1943), in collaboration with British Dame Agnes Gwendoline Hunt (1866-1948), world's first orthopedic nurse, and the Belgian surgeon Albin Lambotte (1866-1955) designed a fracture plate made of stainless steel.[9] The development of implant materials continues with titanium in 1940s and 50s [10] through ceramics

[11,12,13,14,15] to polymers in dentistry and in spinal applications (since the 1980s). [16,17]

Standard manufacturing methods for medical devices are milling and various types of molding. But in the last few years additive manufacturing technologies conquer market shares: For devices used in standard orthopedic applications metal EBM or laser sintering technologies have achieved a status as manufacturing standard.

The authors strongly suggest differentiating various working principles and to classify them according to a risk-based approach inspired by Regulation (EU) 2017/745, Annex 8.

As 3D printed parts manufactured in the medical and medtech environment are intended to be used as (patient matched) implants or (patient specific) instruments, the authors developed a catalogue of safety and performance requirements mandatory for 3D printing technologies and inspired by Regulation (EU) 2017/745, Annex 1.

Regulation (EU) 2017/745 defines different responsibilities and obligations for economic operators in the medical technology environment. For the manufacturer, the most comprehensive requirements apply to design and development, production, marketing and post market surveillance. However, distributors are also held accountable. The user himself is not specifically covered by the regulation with duties and responsibilities. He is often subject to special national obligations, e.g. in Germany the obligations according to the Medical Devices Operator Ordinance (MPBetreibV). However, it is assumed that he uses a product within its intended purpose. Of course, within the scope of his or her freedom of therapy and under certain circumstances, a physician can also use a product outside its intended purpose.

This clear division of roles of the economic actors - legal manufacturer - distributor - user - blurs with the requirement of manufacturing medical devices as point-of-care products. If a user, for example a physician, manufactures, uses and charges for medical devices, obligations of the legal manufacturer and distributor are also transferred to him. In particular, the obligations as described in Regulation (EU) 2017/745 in Articles 13, 14, and 15 in Chapter III and in Annex II should apply. For example, the requirement for a quality management system, the maintenance of a product file, the technical documentation and the obligation to observe the market and to guarantee traceability and to have a vigilance concept implemented. However, there are also certain simplifications for medical devices whose manufacture and use takes place "only within" a healthcare institution, as the Regulation (EU) 2017/745 describes in Art. 5 Sec.5. This does not exempt healthcare institution from extensive requirements for the use, documentation, disclosure, evaluation and monitoring of such in-house manufacture. This exemption will also not apply to every type of product.[18,19]

In the case of point of care solutions, attention must therefore be paid not only to what is technically feasible, but also to what is enforceable in regulatory and legal terms and justifiable in insurance terms. A new verification and validation concept must be developed and put effective to prove mechanical high performance of medical device manufactured with additive manufacturing technologies. There are wide range of parameters that must be defined to ensure a consistent additive manufacturing quality and performance. These parameters vary with respect to (a) different manufacturing methods, (b) different materials but also (c) different geometry of the devices to be manufactured.

Risk Classification 3D Printing Technologies		
Class 1	low risk	3D printing technology using consistently one SIM, pure of sort.
Class 2a	medium risk	3D printing technology combining different SIMs resulting in a composite product or hybrid product.
Class 2b	medium risk	3D printing technology combining different SIMs including bio-chemical materials such as HA, tissue, etc. resulting in a composite product or hybrid product.
Class 3	high risk	3D printing technology combining different SIMs including pharmaceuticals to enable drug delivery or deposition.

Table 2: Risk Classification for 3D printing technologies

Clause	Related MDR Clause	Description
1		3DPTs shall be planned and developed in a structured and documented way. All design and development steps must be reviewed, evaluated, and approved.
1a		Crucial design and development steps must be approved in a risk-based approach. Main design and development must be verified.
1b		3DPT must be validated.
2	SPR 1	3D printing technologies (3DPTs) shall achieve the performance intended by their manufacturer and shall be designed and manufactured in such a way that, during normal conditions of use, they are suitable for their intended purpose. They shall be safe and effective and shall not compromise the clinical condition or the safety of patients or users' safety and health.
2a		3DPT for enhanced osseointegration shall allow for early bone formation and an adherent and dense cell layer.
2b		3DPT for enhanced osseointegration shall allow for high BIC with a balanced ratio of old "parent" bone and new bone.
3	SPR 10.1	3DPTs shall be designed and manufactured in such a way as to ensure that the characteristics and performance requirements referred to in MDR, Annex 1, Chapter I are fulfilled. Particular attention shall be paid to:
3a		the choice of materials and substances used, particularly as regards toxicity and biocompatibility, metabolic reactivity;
3b		the compatibility between the materials and substances used and biological tissues, cells, and body fluids, taking account of the intended purpose of the 3DPT and, where relevant, absorption, distribution, metabolism, and excretion;
3c		the mechanical properties of the 3DPT on the implant, reflecting, where appropriate, wear-resistance and abrasion;
3d		surface properties such as homogeneity and (layer) thickness
3e		the confirmation that the 3DPT meets any defined chemical and/or biological specifications.
4	SPR 10.2	3DPT modified devices shall be designed, manufactured, and packaged in such a way as to minimize the risk posed by contaminants and residues to patients, taking account of the intended purpose of the device, and to the persons involved in the transport, storage, and use of the devices. It must be taken into account that packaging materials may react with 3DPT.
4a		Confirmation that packaging material does not interact with or react to 3DPT.
5	SPR 10.4.1	3DPTs shall be designed and manufactured in such a way as to reduce as far as possible the risks posed by substances or particles, including wear debris, degradation (products), and processing residues that may be released from the 3DPT.
6	SPR 10.6:	3DPTs shall be designed and manufactured in such a way as to reduce as far as possible the risks linked to the size and the properties of particles, which are or can be released into the patient's or user's body unless they come into contact with intact skin only. Special attention shall be given to nanomaterials.
7	11.1	3DPTs and their manufacturing processes shall be designed in such a way as to eliminate or to reduce as far as possible the risk of infection to patients, users and, where applicable, other persons. The design shall:
7a		allow easy and safe handling,
7b		as far as possible, avoid any microbial leakage from the device and/or microbial exposure during use, and
7c		prevent microbial contamination of the device or its content such as specimens or fluids.
8	11.2	3DPTs shall be designed to allow for safe cleaning, disinfection, and/or sterilization.
9	SPR 12.2	Devices that are composed of substances or of combinations of substances that are intended to

Clause	Related MDR Clause	Description
		be introduced into the human body, and that are absorbed by or locally dispersed in the human body shall comply with the relevant requirements laid down in Annex I to Directive 2001/83/EC for the evaluation of absorption, distribution, metabolism, excretion, local tolerance, toxicity, interaction with other devices, medicinal products or other substances and potential for adverse reactions, as required by the applicable conformity assessment procedure under this regulation.
10	SPR 13.2	For 3DPTs manufactured utilizing tissues or cells of animal origin, or their derivatives, which are non-viable or rendered non-viable the following shall apply:
10a		where feasible taking into account the animal species, tissues, and cells of animal origin, or their derivatives, shall originate from animals that have been subjected to veterinary controls that are adapted to the intended use of the tissues. Information on the geographical origin of the animals shall be retained by manufacturers;
10b		sourcing, processing, preservation, testing, and handling of tissues, cells, and substances of animal origin, or their derivatives, shall be carried out in a way as to provide safety for patients, users and, where applicable, other persons. In particular, safety with regard to viruses and other transmissible agents shall be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process, except when the use of such methods would lead to unacceptable degradation compromising the clinical benefit of the device;
10c		in the case of 3DPTs utilizing tissues or cells of animal origin, or their derivatives, as referred to in Regulation (EU) No 722/2012 the particular requirements laid down in that Regulation shall apply.
11		3DPT shall meet labelling requirements clearly highlighting the methods used to verify and validate the safety and performance of the respective 3DPT
12		Where applicable, 3DPTs must meet all SPRs stipulated in MDR, Annex 1.

Table 3: Essential safety and performance requirements for 3D printing technologies

Examining e.g. FFF technology, nozzle diameter, nozzle temperature and printing speed must be analyzed and defined per material and geometry. The nozzle diameter is considered to be the most significant parameter affecting the bending and compression performance of the printed PEEK samples, followed by printing speed and nozzle temperature[1].

Conclusion. To display verification and validation results in a transparent and comparable approach, the authors have defined a scoring system: The Safety and Performance Evidence Level (SP Evidence Level for 3DPTs) Scoring System (S.P.E.L.).

The scoring system (Table 4) defined in this publication does not assess the values and results of the verification and validation activities performed, but starts at a fundamental level: the scoring system does not assess the individual test results, but rather the "evidence level" of the underlying verification and validation strategy. Thus, it is possible to relate each result to the verification and validation strategy and better assess the overall evidence level.

With this scoring system, data of 3D printing technologies are transparently displayed, and test methods aligned to such an extent that the potential user - surgeon or patient - can compare different technologies with each other.

A quality seal - issued by a neutral authority, such as a certification authority or Notified Body, accredited for the evaluation of medical devices and quality management systems - could provide the necessary transparency. The quality seal shall indicate in combination (i) the 3D printing method according to Table 1 (ii), the risk profile / risk classification of the 3DPT according to Table 2, (iii) the material incorporated and (iv) the Safety and Performance Evidence Level and its degree of fulfillment for the respective 3DPT according to Table 4.[1]

This scoring system is the first attempt to establish a standardized and transparent test system for the quality of 3DPT products and is divided into 4 subsections: Design and development, manufacturing, mechanical testing, clinical applicability. In each subsection a maximum evidence level of 100 % can be reached. Note: Every subsection (sections I-IV) only represents 25% of the overall evidence level (degree of fulfillment). The overall evidence level can reach a maximum of 100% and is calculated as follows: [e1(0,25)*(XX%) + e2(0,25)*(XX%) + e3(0,25)*(XX%) + e4(0,25)*(XX%)] = XX %.

			Grading System	Impact Score	Degree of Fulfillment
eI	**Design and Development (only one answer possible. Max: 3 points = 100 %)**				
	Design and Development	Verified and validated & certified ISO 13485	YES NO	3 0	100 %
		Verified and validated & according to GMP standard	YES NO	2 0	66 %
		Verified and validated	YES NO	1 0	33 %
		No Validation	YES NO	0 0	0 %
			Subtotal		100 % (1/4)
eII	**Manufacturing Method (only one answer possible. Max: 3 points = 100 %)**				
	Manufacturing Process	Manufacturing process (industrial scale) is verified and validated & ISO 13485 certified	YES NO	3 0	100 %
		Manufacturing process (industrial scale) is verified and validated & according to GMP standard	YES NO	2 0	66 %
		Patient matched concept verified and validated	YES NO	1 0	33 %
		Patient matched concept not verified and validated	YES NO	0 0	0 %
			Subtotal		100 % (1/4)
eIII	**Pre-clinical Testing: Abrasion and Delamination (only one answer possible. Max: 3 points = 100 %)**				
	Mechanical Testing	Rationale & verified and validated & performed by an accredited laboratory	YES NO	3 0	100 %
		Rationale & verified and validated	YES NO	2 0	66 %
		Rationale	YES NO	1 0	33 %
		Other	YES NO	0 0	0 %
		None		FAILED	
			Subtotal		100 % (1/4)
eIV	**Applicability (only one answer possible. Max: 3 points = 100 %)**				
	Limitation of clinical applicability	Surgical technique, storage, packaging, cleaning, and sterilization requirements of the implant made with 3DPT are not affected by 3DPT.	YES NO	4 0	100 %
		Only storage conditions of the implant made with 3DPT must be adapted to the requirements of 3DPT.	YES NO	3 0	75 %
		Storage, packaging, cleaning, and sterilization conditions of the implant made with 3DPT must be adapted to the requirements of 3DPT.	YES NO	2 0	50 %
		Surgical technique must be adapted to the requirements of 3DPT.	YES NO	1 0	25 %
		3DPT cannot be stored using standard storage conditions guaranteeing a shelflife of (>/=) 5 years	YES NO	0 0	0 %
			Subtotal		100 % (1/4)

Table 4: Safety and Performance Evidence Level (SP Evidence Level for 3DPTs)

With this scoring system, the significance and applicability of verification and validation procedures can be determined that have been carried out to evaluate the marketability of a 3DPT. Thus an evaluation platform was created, which can be used system-independently of country-specific regulations (EU:MDR / US:FDA / China:cFDA / Brazil:ANVISA, etc.), in order to make comparable and transparent statements regarding the significance of test results.

Our current focus lies on polymer implant materials, but the principle can easily be adapted to all 3D printable materials. Of course, the future will show the applicability of the scoring system and adaptations might become necessary but what is essential is that the here suggested system is the first step towards a transparent evaluation of 3D printed medical devices.

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