Bentley InnoMed GmbH
Lotzenäcker 3
D - 72379 Hechingen, Germany
www.bentley.global

fon + 49 (0)7471 984 995 10
fax + 49 (0)7471 984 995 9
mail info@bentley.global

Bentley InnoMed GmbH, Lotzenäcker 3, D - 72379 Hechingen

Trade Register Stuttgart: HRB420936
VAT ID-No. DE 225487186
CEO: Sebastian Büchert

Date
12.05.2023

Concerning
Comments for Annex XV restriction report - Per- and polyfluoroalkyl substances (PFAS)

Dear Madam or Sir,

Bentley InnoMed GmbH - a medical device company manufacturing class III and class IIb products for the endovascular treatment of severe, life-threatening vascular afflictions - wants to give its comment and therefore participate in the open consultation of the ECHA regarding the restriction on the manufacture, placing on the market and use of PFASs.

Within this document, detailed information is provided how a general restriction on PFAS impacts Bentley, the health care system, hospitals and patients.

Christian Bader
Director Quality and Market Access

Terms and Glossary

Abbreviation	Full Form
BGA	BeGraft Aortic Stent Graft System (Bentley Product)
BGC	BeGraft Coronary Stent Graft System (Bentley Product)
BGP	BeGraft Peripheral Stent Graft System (Bentley Product)
BGP+	BeGraft Peripheral Plus Stent Graft System (Bentley Product)
BSP	BeSmooth Peripheral Stent System (Bentley Product)
BYV	BeYond Venous Self-Expanding Stent System (Bentley Product)
ePTFE	Expanded Polytetrafluoroethylene
MDD	Medical Device Directive
MDR	Medical Device Regulation, i.e. Regulation (EU)2017/745
PFAS	Per- and Polyfluoroalkyl Substances
PTFE	Polytetrafluoroethylene
TPU	Thermoplastic Polyurethane
UHMW-PE	Ultra High Molecular Weight Polyethylene

General information

Bentley is an international medical technology company with headquarters in Hechingen, Germany.
At Bentley, innovative products for the endovascular treatment of severe, life-threatening vascular afflictions are developed and manufactured. All products are classified as class III or class IIb products according to the MDR. Today, Bentley products are available in more than 80 countries. Since the launch of Bentley's first product in 2012, the stent (grafts) have been widely adopted and Bentley is market leader in several European countries. In 2023, Bentley will manufacture around 120,000 implants, mainly so called stent grafts that consist of a metal scaffold structure and a polymeric cover made from expanded polytetrafluoroethylene (ePTFE). The implants are sold in an assembly with a delivery system the implants are mounted onto/into. The delivery system comprises also polytetrafluoroethylene (PTFE) components whose function is described in detail in the following argumentation.

In the following, the PTFE usage has been calculated in kg for two components being used the most within our products and therefore accounting for the largest share by weight.

For the manufacturing of the implant covers, 6.6 kg of expanded PTFE (ePTFE) are annually used within the Bentley process chain. This small amount of ePTFE helps treating tens of thousands of patients from physical suffering and preventing death of them.

To manufacture the protective sheaths of the delivery system, there is annual consumption of 39.6 kg of PTFE in form of tubing.

Referring to the ECHA restriction proposal on PFAS substances, all of the Bentley life-saving and emergency products will be affected by the restriction of PFAS, as all products contain PTFE. As we are certain that the socio-economic impact of the proposed regulations will dramatically affect patient safety and deteriorate quality of medical treatment, we submit our thoughts towards the restriction of PTFE in medical applications and give an argumentation why we do not see any alternative in substituting PTFE.

Overview of PFAS substances used

The only PFAS substance used within Bentley products is PTFE. PTFE is a long-chain, polymeric and solid representative of PFAS substances. Opposite to other gaseous or liquid PFAS substances, PTFE is highly inert and therefore, non-mobile, non-toxic, non-accumulative and non-soluble. The material has outstanding properties in terms of mechanical, physical and electrical behavior. Some of them are crucial for an adequate function of a state-of-the-art vascular stent graft and its corresponding delivery system. The unique properties of PTFE indispensable when manufacturing a stent graft are given in the following list:

- proven biocompatibility of PTFE and ePTFE graft material with long-term use in vascular implants
- long-term evidence for safe clinical use in implant applications
- low stiffness of the polymer with very high plastic strain at low stress values (see Figure 1)
- durability and chemical stability in challenging environments
- low coefficient of friction
- ability to expand the material (allows manufacturing of ePTFE with fibrillary structure)

To continue the list, special properties of ePTFE are listed:

- non-textile porosity
- semi-permeability while maintaining fluid/blood tightness (even expanded)

PTFE components in the manufacturing of vascular implants

In the table below, all components of Bentley stent (graft) systems are listed that are concerned of the ANNEX XV RESTRICTION REPORT regarding PFAS.

The affected product components are assigned to different use sectors (with sub-uses), as the duration of the pending derogations refers to the application of PFAS.

Table 1: Within the restriction affected products

Use sector (with sub-uses)	Affected Products	Affected Product Components
Implantable medical devices	BGP, BGP+, BGC, BGA, R&D Products	ePTFE Graft / Cover
Tubes and catheters	BGC, BGA, BYV, R&D Products	Delivery System, Catheter Tubing
Packaging of medical devices	BGP, BGP+, BGA, BSP, R&D Products	Stent Protective Sheaths, Balloon Protective Sheaths

Justification for the use of ePTFE and PTFE

For many years PTFE has been used within several medical devices: medical implants (e.g. stent grafts or artificial heart valves), catheters, stylets or instruments for endoscopic surgery. Through the long-term application of a large variety of products there is well-known evidence on excellent clinical outcomes of medical devices using PTFE, sometimes directly linked to the PTFE properties that allow the product functionality for an explicit device or procedure.

In the following, looking at the function of a stent cover, the necessity for the use of ePTFE is discussed in detail before assessing the beneficial influence of PTFE use on the different tubing and packaging components.

ePTFE has an excellent stability against hydrolytic and oxidative degradation in the long-term blood-contact environment in the vascular system. As the material is bio-inert, no leaching of potentially toxic degradation products can occur. The unique, fibrillar structure of ePTFE mimics components of the extra cellular matrix and therefore supports ingrowth of cells into and through the graft material, enhancing biocompatibility and lowering risk for acute thrombosis or restenosis. At the same time, the graft material shows sufficient fluid tightness to prevent any blood extravasation from the inner lumen of the stent graft which is crucial in many indications of the stent grafts, for example in the treatment of vascular ruptures or aneurysms.

The most important fact for the use of ePTFE as stent cover is the stress-strain behavior of the material. PTFE in general can carry very large plastic deformations at low stress levels. The fact that PTFE can be expanded to ePTFE in a special thermo-mechanical stretching process also belongs to those low-stiffness properties. ePTFE semi-finished products can be further lengthened, more easily in perpendicular direction to the fibrils. Further expansion of the ePTFE tubing (stent cover) is necessary during the expansion of the stent graft. As the metal scaffold structure is dilated by the balloon of the delivery system, the diameter and consequently the circumference of the implant increases by factor 2 and the graft material needs to follow that expansion. The excellent expansion behavior of ePTFE can be seen in Figure 2. The graft expansion shall proceed under stress levels as low as possible, as the balloon pressure is limited (see low stress level of PTFE compared to other material options in Figure 3). Ideally, the graft material shall plastically deform during the expansion. If the material is plastically deformed for the most part, there is just slight elastic recoil of the graft material that applies a force onto the scaffold in opposite expansion direction. A low elastic recoil of the whole stent graft is desired as recoil of a stent graft negatively affects the handling of the device and impedes safe fixation of the implant. Additionally, a stiffer material would decrease the flexibility of the stent graft mounted (crimped) onto the delivery system. This would lower the usability of the product and prevent the safe feasibility of some procedures as the stent graft could not be tracked through tortuous anatomies anymore.

Looking at the delivery system applications of PTFE tubing, the low-friction properties of PTFE are very important and explained along two examples:

Within the delivery system of the self-expanding BYV stent, the use of PTFE inner tubing allows the easy implantation of the stent, as the very low coefficient of friction of the PTFE tubing reduces the push-out-force of the stent off the delivery system. Other materials with a higher friction could result in particle generation through abrasion entering the patient’s organism. In the organism, particles could occlude small peripheral vessels or if occurring in the venous system even lead to emboli in the brain. This would be an iatrogenic complication.

In the delivery system of the BGA stent graft, a so-called applicator made from PTFE is contained. This applicator is crucial for a safe placement as it is dedicated to lower the friction when guiding the

stent graft crimped onto the balloon through the hemostatic valve of the introducer sheath. Without the use of the low-friction applicator, the stent can be loosened and the surgeon will not be able to precisely implant the stent anymore causing additional retrieving and removal of the stent, increasing the duration of the procedure and putting risk to the patient.

Due to the same reason, the protective sheaths to protect the crimped stents / stent grafts on the balloon are made from PTFE. The low friction material allows removal of the narrow protective sheath that constraints the stent to the balloon during transport without loosening the stent from the balloon. In consequence, there is reduced risk for stent translation on or dislodgement from the balloon.

Market analysis and assessment on alternative materials

Analyzing the direct competitor products of the BeGraft product family, it is obvious that – besides one exception – there is no CE-approved product with a graft material different to ePTFE. The only exception is a stent graft covered by electrospun thermoplastic polyurethane (TPU). This product covers only the indications of the BGC stent graft in cardiovascular applications. Peripheral arteries or the aorta cannot be treated by the TPU-covered device due to a lack of available large-size stent grafts.

Furthermore, the chemical stability in terms of hydrolysis and oxidation resistance is far below that of PTFE. Long-term blood contact applications with a service lifetime of above ten years are challenging considering TPU as an alternative material to ePTFE. It is unclear whether mechanical integrity – crucial for the graft material considering the treatment of ruptures or aneurysms – will persist over ten years, thus limiting the possibility to use TPU as graft material. Compared to a durable material like ePTFE, this would result in either an early replacement of the already implanted stent or the stent not covering the ruptures or aneurysms anymore leading to the death of the patient.

Besides the implications on chemical stability, the mechanical behavior of TPU would negatively affect stent performance and safety.

Since in the manufacturing of stent grafts, the stents have different diameters in the various process steps. The covering material must be able to undergo all these diameter variations, from the crimped stage to the final expanded stent in the vessel, without losing its functional properties to ensure proper implant fixation. As already mentioned above, ePTFE undergoes the expansion under plastic deformation. Consequently there is almost no residual stress within the graft material after the expansion. Opposite to that, TPU graft material would undergo elastic strain during expansion. Finally, there will be a residual stress within the graft material due to the elastic recoil of the TPU material. This recoil of the graft would apply a force on the metal scaffold, narrowing down the diameter of the implant which is undesired. Other graft materials like Dacron® or polyethylene – commonly used in the manufacturing of aortic endografts – are not suitable in the construction of balloon-expandable stent grafts as they are neither able to carry the necessary high strains plastically, nor elastically.

In consequence, we do not see any viable alternative to ePTFE as graft material.

Socio-economic impact of the planned restriction

Besides the purely technical argumentation, some more general points to consider concerning the PFAS restriction in the context of medical devices have to be mentioned.

The time until a new product with known materials is available in the EU (MDR-approved) has shown to be more than seven years. The development of an alternative material with equal properties to substitute PTFE required basic research with uncertain outcome and unknown time consumption. Additionally, the approval process of the new substance itself will consume years before being able to start a product development process. The approval process for medical devices, especially for permanent implants of all sorts in all markets worldwide, using new, completely unknown properties within the dedicated application requires an undefined amount of time. This is due to the fact that the regulations for medical devices worldwide require sound investigation of the material, both, in vitro and in vivo i.e. animal testing, but particularly in humans as part of clinical control studies before submission to the notified bodies. Clinical studies are not only highly regulated involving many instances like ethics committees, competent authorities, hospital physicians and adequate patients but are extremely time consuming as most of the involved steps can only be performed one after the other after the medical device has been finally designed. In consequence, the actually conceded 13.5 years derogation for the use of PFAS in medical implants is by far not sufficient to get approval for new products consisting of newly developed, ground-breaking materials. It must be taken into account that the notified bodies by far did not conclude the MDR approval of former MDD devices and there is a large deficiency in personnel capacities of the notified bodies, critically delaying the MDR approval of persisting products. For the next years, there will not be sufficient capacities of the notified bodies to carry out approval of products of completely new substances.

Finally, after the 13.5 years derogation, no more stent grafts for the given indications could be commercially sold, as all competitors also underlie the PFAS restriction due to their graft material selection. A regress in terms of endovascular procedures would subsequently follow with the necessity for open surgery and slower recovery of the patients, thus increasing costs for the health care system. Shorter hospitalization is highly preferred due to hospital staff utilization (e.g. see COVID). Additionally, synthetic grafts for open surgery are also very often made from ePTFE so that a conversion back to open surgery will not minimize PTFE consumption.

As the successful substitution of PTFE and ePTFE by currently non-known materials is highly uncertain, there is also the risk for Bentley to lose the whole product spectrum, causing thousands of patients suffering from deteriorated medical treatment or even losing their life through non-availability of adequate medical devices. To give an impression of the importance of the products: the BGA implant has an estimated market share of 80% in its product group for the given indications and there is no viable alternative to that product, especially none containing no ePTFE covering.

Based on the given facts, we propose to give a general time-unlimited derogation for PTFE. This proposal is based on the fact that PTFE is a PFAS substance of no concern to human health or the environment (see also the following section **Situation of PFAS restrictions in non-EU countries**).

Ordered quantities are very low in the medical industry (see for example the annual PTFE consumption of Bentley). If just the medical device industry got a time-unlimited derogation, the supply chains of PTFE would become very weak, as many chemical companies synthesizing PTFE resin and many PTFE processors rejected their production of raw materials and semi-finished products due to unprofitable annual production. Consequently, this would just be a theoretical derogation for the medical industry, as the supply chains collapsed. This process has already begun as former PTFE resin

suppliers will stop their production in the foreseeable future, leading to material changes for the medical device industry that are complicated from a regulatory point of view.

Assessment on PFAS emission potential

A potential emission of PFAS within the Bentley process chain was assessed. Along the process chain there is no risk for PFAS emission as the semi-finished ePTFE tubing is only cut in sections of the necessary length and then the metal scaffolds are covered by those ePTFE tube sections. There is no risk for degradation or abrasion of the ePTFE covers. The PTFE protective sheaths and tubings used in the delivery system are also bought as semi-finished parts and just assembled. There is also no risk for degradation or abrasion of PTFE that could release PTFE particles or short-chain PFAS substances.

Situation of PFAS restrictions in non-EU countries

The Australian Government PFAS task force is responsible for whole-of-government coordination and oversight of Australian Government responses to PFAS contamination. On their website the PFAS task force states the following:

"Teflon™ is a trade name for the chemical 'polytetrafluoroethylene' (PTFE). PTFE is a member of the PFAS family but it has a different structure from PFOA, PFOS or PFHxS, which gives it different properties.

There are several important differences between the properties of Teflon (PTFE) and PFOA/PFOS/PFHxS:

- *PTFE is not soluble in water - PFOA, PFOS and PFHxS are soluble in water.*
- *PTFE is too large and too insoluble to be absorbed by organisms - PFOA, PFOS and PFHxS are readily absorbed by organisms that eat/drink contaminated food/water.*
- *PTFE is not toxic to animals - PFOA, PFOS and PFHxS have a range of toxic effects in animals.*

These differences mean that regulators do not consider PTFE (Teflon) to be a chemical of concern to human health or the environment.

The link between PFOA and Teflon is that PFOA is used to help make Teflon. However, it is important to emphasis that PFOA is not an ingredient in Teflon - it is simply added to the reaction vessel to help make Teflon, and is removed at the end of the process. Therefore, Teflon should not contain PFOA. There are strict standards in place to help ensure that Teflon does not contain PFOA."

Conclusion

To conclude, a general unlimited derogation for the use of PTFE is proposed. There is no viable substitute for PTFE in the foreseeable future equaling only some of the unique properties of PTFE (and other fluoropolymers). For PTFE, the undenied hazardous potential of many PFAS is not seen, as the long-chain PTFE molecule is highly inert, non-mobile, does not accumulate and is non-toxic. It was evidently shown that the functionality of modern balloon-expandable stent grafts is directly linked to the PTFE material properties in most aspects. Additionally, our concerns on collapsing supply chains were discussed if there was just a time-unlimited derogation for PTFE in the medical device industry. Taken these facts together, there is enough evidence to justify the further use of PTFE on the base of a benefit-risk analysis. Quality of medical treatment and patient outcomes would deteriorate as a direct consequence of a PTFE restriction.

Annex

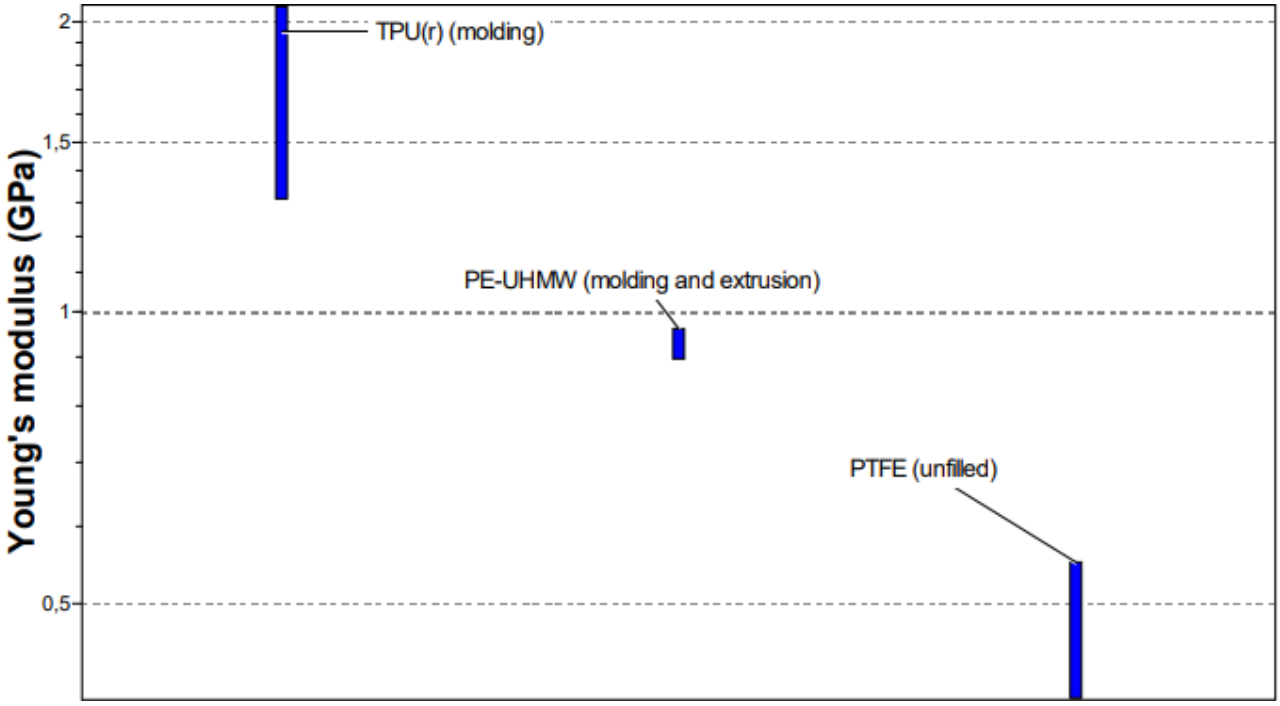

Figure 1: Young's modulus of PTFE in comparison to TPU and PE-UHMW

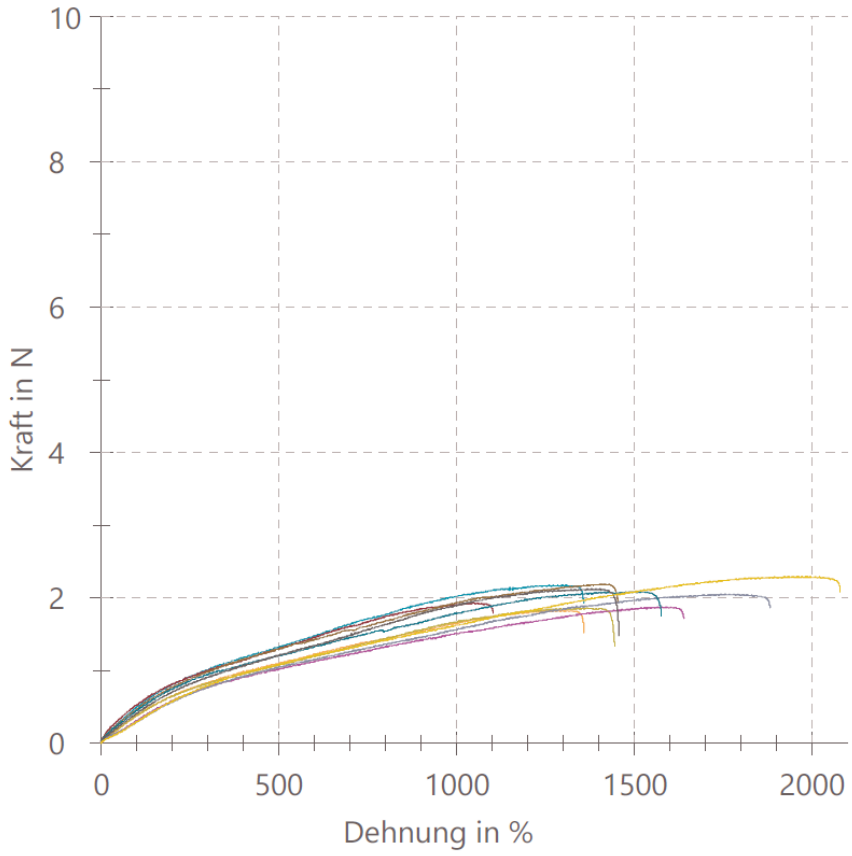

Figure 2: Tensile test diagrams (internal testing) of ePTFE graft material samples in tensile direction perpendicular to the fibrils

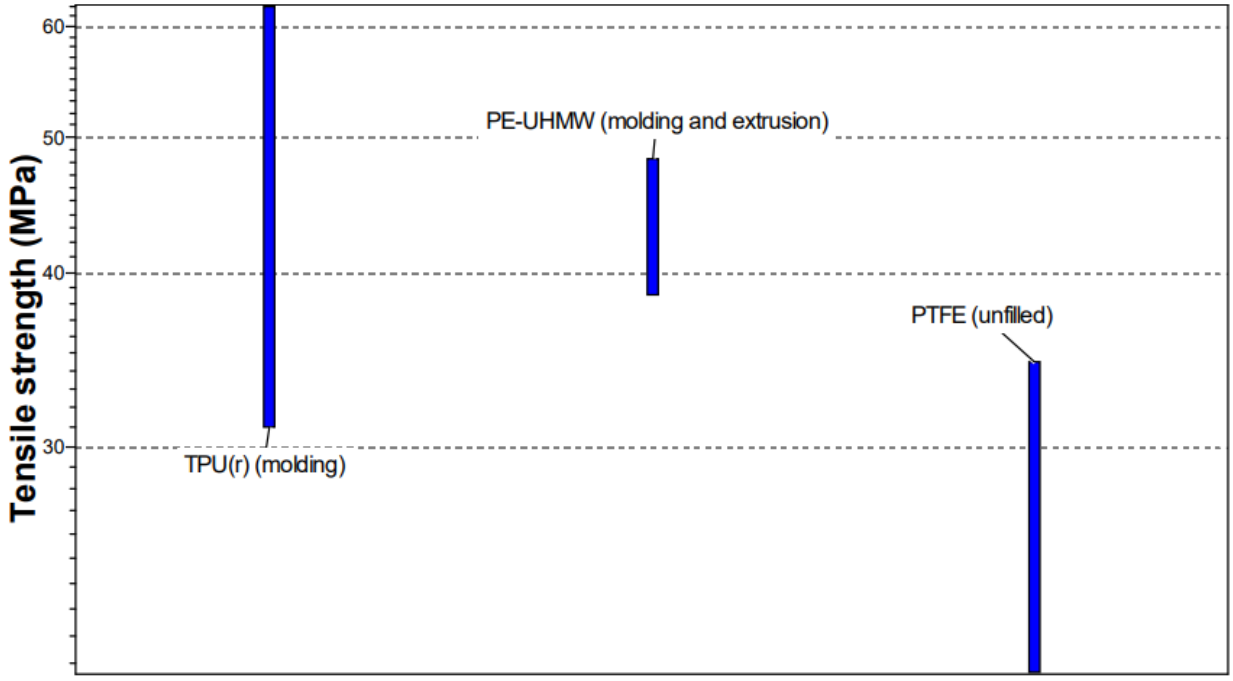

Figure 3: Tensile strength of PTFE in comparison to TPU and PE-UHMW