Pharmpur GmbH · Messerschmittring 33 · 86343 Königsbrunn

Comment to PFAS Restriction Proposal Consultation – Pharmpur GmbH, Germany

Commentator: Pharmpur GmbH

Messerschmittring 33, 86343 Königsbrunn

www.pharmpur.de

www.ophthafutur.de

Contact Person: Dr. Andreas Hofmann

Head of Regulatory Affairs, PRRC (MDR Art. 15)

[redacted]@pharmpur.de

Purpose

Request listing of Perflunafen, Perfluorooctane, Hexafluoroethan and Octafluoropropan in the sub-use implantable medical devices

Description of the Products Marketed

The above mentioned materials are used as key component for the manufacture of products, which are substantial implantable Medical Devices, i.e., ocular endotamponades acc. to ISO 16672 and are used in retinal surgery. Each of our products consists of 100% of one the ultra-purified (inhouse process) substances mentioned above. These substances are **active substances** within the definition of medical devices, i.e., they are acting physically acc. to their special chemical/physical properties.

Pharmpur as a legal manufacturer as well as contract manufacturer has a market share within the EEA market of of more than 20% for eye surgery products for vitreoretinal surgery and is marketing its products world-wide.

Our Proposal for Reclassification of the Derogation of these Substances for Use as Ophthalmic Endotamponades (Medical Devices)

Based on the data and facts presented in this comment and due to the fact that these substances are **active substances** within the definition of medical devices, i.e. they are acting physically acc. to their special chemical/physical properties, we recommend that these **vital products** are listed in **RO2, paragraph 4 as a new clause d) for a derogation without time limit**. In absence of alternatives, as presented in section "Current Status of R&D for Alternatives" in this comment, a derogation period of 12 years is too short for the evaluation of alternatives.

Substances within the scope of this comment:

General	
INN	Perflunafen
Synonyms	Perfluorodecalin Perfluoroperhydronaphthalene PERFLUORODECALIN (INCI)
Molecular Formula	$C_{10}F_{18}$
CAS Codes	
CAS	306-94-5 60433-11-6 (cis) 60433-12-7 (trans)
Molecular Mass	
Molecular Mass	462.08 $g \cdot mol^{-1}$

General	
INN	Perfluorooctane
Synonyms	Octadecafluorooctane 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Octadecafluorooctane PF5080
Molecular Formula	C_8F_{18}
CAS Codes	
CAS	307-34-6
Molecular Mass	
Molecular Mass	438.06 $g \cdot mol^{-1}$

These two substances above are used in other indications as medical devices as well:

Application	Fully-fluorinated alkane	Where	Example reference
Blood extender	Perfluorodecalin	Blood	"Perfluoro Compounds as Blood Extender", JG Reiss, M Le Blanc, Angewandte Chemie, 17(9), 1978, p621-700.
Wound healing	Perfluorodecalin	Skin	A new treatment for ischemic ulcers: foot bath therapy using high oxygen soluble fluid Iwai et al., J Cardiovasc Surg (Torino). 1989 May-Jun;30(3):490-3.
Liquid breathing	Perfluorodecalin	Lungs	Early perfluorodecalin lung distension in infants with congenital diaphragmatic hernia GM Walker et al, J Pediatr Surg. 2003 Jan;38(1):17-20; discussion 17-20
Ulcer treatment	Perfluorodecalin	Foot	A new treatment for ischemic ulcers: foot bath therapy using high oxygen soluble fluid. Iwai T, Sato S, Yamada T, Muraoka Y, Sakurazawa K, Inoue Y, Kinoshita H, Endo M. J Cardiovasc Surg (Torino). 1989 May-Jun;30(3):490-3.
Tattoo removal	Perfluorodecalin	Skin	http://www.aslms.org/professional/documents/EditorsChoiceLSMFeb45.2.pdf
In-vitro fertilisation (IVF) Treatment	Perfluoroctan	Spermatocyte carrier	Currently in application

General	
INN	Hexafluoroethane
Synonyms	1,1,1,2,2,2-Hexafluoroethane
Molecular Formula	C_2F_6
CAS Codes	
CAS	76-16-4
Molecular Mass	
Molecular Mass	138.01 $g \cdot mol^{-1}$

General	
INN	Perfluoropropane
Synonyms	1,1,1,2,2,3,3,3-Octafluoropropane Perflurane
Molecular Formula	C_3F_8
CAS Codes	
CAS	76-19-7
Molecular Mass	
Molecular Mass	188.02 $g \cdot mol^{-1}$

Affected Stakeholders of Ocular Endotamponades in the EU

In the EU, including Pharmpur, 9 companies (D.O.R.C. (Netherlands), Carl Zeiss Meditec (Germany), Arcadophta (France), FCI S.A.S (France), Geuder AG, (Germany), Alchimia S.r.L. (Italy), Micromed S.r.L. (Italy), Bausch&Lomb (Germany), Pharmpur GmbH (Germany)) are on the market with these products and are directly or indirectly affected by the Restriction Proposal for PFAS.

Current Derogation in the Restriction Proposal

According to A.3.10.1.1 and Table A.99 in the current Restriction Proposal, neither the ocular endotamponades as implantable medical devices are listed or mentioned there, nor the substances described above. In RO2, paragraph 6 only fluoropolymers and perfluoropolyethers used as implantable medical devices are listed for a time limited derogation of 13.5 years.

Therefore, we recommend listing these substances in the sub-use implantable medical devices.

Production Data

Currently these ocular endotamponades make 22% of annual produced units of Pharmpur's overall product portfolio.

Annual production within the EEA market from Pharmpur is more than 2 tons (Perfluorodecalin = 1.3 tons; Perfluorooctane = 0.8 tons; Perfluoropropane = 0.1 tons; Hexafluoroethane = 0.1 tons).

Downstream users are health care professionals at Public Hospitals, Private Clinics, University Clinics, and Eye Surgery Ambulances.

Data of Clinical Use in Surgeries within the EU

About 1 million surgeries within three years within the EEA.

Eye surgery in the posterior segment of the eye.

Application of the Substances and Medicinal Background for the Use

Hexafluoroethane and octafluoropropane, both perfluorocarbon gases, as well as perfluorodecalin and perfluorooctane, both perfluorocarbon liquids (PFCLs) are classified as ophthalmic implants - ocular endotamponades (OEs) and the international standard EN ISO 16672 applies. According to EN ISO 16672, OEs are "a group of non-solid surgically invasive medical devices introduced into the vitreous cavity of the eye to flatten and position a detached retina onto the retinal pigment epithelium (RPE), or to tamponade the retina". "They are used either intra-operatively and removed at the end of surgery, as in the case of perfluorocarbon liquids, or are designed to remain in the vitreous cavity until removal at a later date as in the case of silicone oils, or they are completely absorbed as in the case of gaseous OE." From this citation of the actual 3rd edition of the EN ISO 16672 (from 2021) it becomes clear, that even nowadays only three classes of OEs exist: 1) PFCLs, 2) silicone oil, and 3) gaseous OE. This is paralleled by a recent publication (Kohli & Tripathy 2023) containing a categorisation based on the surgical or functional application of agents for vitreous tamponade: "a) To replace the vitreous during the surgery: saline, ringer lactate, and balanced salt solution (BSS); b) To assist during the surgery as a surgical tool (third hand of the retinal surgeon): perfluorocarbon liquids (PFCL); c) To provide postoperative tamponade: air, sulfur hexafluoride (SF_6), perfluoroethane (C_2F_6), perfluoropropane (C_3F_8), and silicone oil (SO)" *(agents not freely interchangeable – selection according to disease, severity, patient characteristics: different duration times [air with only very short-term duration, 1 day], unique benefits & risks [SO reserved for severe cases due to the numerous and partially serious side effects associated with its use as well as to the required second intervention for removal associated with complications as well (Mohamed S, Lai TY (2010); Hammer, M.E. (2016); Schulz A, Szurman P. (2022))]).*

As an intraoperative tool in vitreoretinal surgery, **PFCLs** (as medical devices **perfluorodecalin** & **perfluorooctane**) have been established since the 1980s for the hydrokinetic manipulation of the detached neurosensory retina. Especially in complicated retinal detachments where the

neurosensory retina may be completely detached, folded or even be in a funnel-shaped configuration (up to a closed funnel) hydrokinetic unfolding, flattening and reattachment of the highly vulnerable neurosensory retina accompanied by drainage of the underneath accumulated fluid by using PFCLs is indispensable. Additionally, PFCL also stabilises the retina during procedures for removal of tractions to the retina posed by pathological membranes (Bourke 1995, *from Chang 1987 & 1988*; Kohli & Tripathy 2023 – complicated conditions: proliferative vitreoretinopathy, diabetic retinopathy). As an example, before the introduction of PFCL rhegmatogenous retinal detachment associated with giant retinal tears was extremely difficult to treat – the surgery was done on a Stryker table (inverted surgical table/bed) requiring the patient to be enrolled into a prone position to unfold the retina (Kohli & Tripathy 2023) and retinal tacks had to be used to fix the retina to the wall of the eye mechanically (Berrocal et al. 2017). Prior to the use of PFCLs, retinal reattachment was achieved by fluid-air exchange only but, with a few exceptions, requiring a posterior drainage retinotomy to remove the subretinal fluid as air replaces the subretinal fluid posteriorly and the retina laterally. While residues of subretinal fluid loculated posteriorly are of little consequence for retinal reattachment as long as the retinal break is closed as remaining subretinal fluid will be removed from the subretinal space by the pump function of the retinal pigment epithelium, posteriorly subretinal fluid exerts a pull on the anterior retina (Wong 2007). One of three effects can result from this: 1) stretching of the retina resulting in limited macular translocation, 2) folding of the retina – iatrogenic retinal folds – often passing through macula and cause reduction of visual acuity and often are accompanied by disturbing symptoms of distortion, 3) slippage of the retina (Wong 2007). Posterior drainage retinotomy can be associated with significant complications, including haemorrhage, fibrosis with traction, choroidal neovascularisation, and visual field loss (Abrams et al. 2013). In contrast to air, PFCL replaces the subretinal fluid anteriorly and can thereby avoid the need for posterior drainage retinotomy (Bourke 1995). Filling with PFCL is performed up to the most anteriorly located retinal break(s) to allow for drainage of the subretinal fluid through the retinal break(s). PFCL use reduces the likelihood of posterior retinal slippage in the management of giant retinal tears (Bourke & Cooling 1995). PFCL minimises macular distortion or folds (Regillo & Mahrous 2021). Laser application is used to permanently fix neurosensory retinal areas with the underlying retinal pigment epithelium by formation of scars (eg. edges of retinal breaks). Although laser application can be performed under air, PFCLs are considered a safe medium for laser energy delivery since they do not absorb visible light and have a higher boiling point than irrigation fluid (Bourke & Cooling 1995).

Further indispensable intraoperative applications of PFCLs are (Kohli & Tripathy 2023): 1) In ocular trauma PFCLs enable the removal of intraocular foreign bodies (IOFBs) while preventing the

vulnerable neurosensory retina. While metallic IOFBs may be removed using its magnetic properities, in particular non-metallic IOFBs rely on mechanical removal. 2) In ocular trauma as well, PFCL can be useful in the removal of incarcerated retina. 3) dislocated crystalline or intraocular lenses can be floated with PFCL to the mid-vitreous cavity (lift up) for safer removal with protected vulnerable neurosensory retina.
For practical routine clinical use it is concluded (Feltgen & Hoerauf 2019): "Heavy fluids have become an indispensable intraoperative aid in vitreoretinal surgery and have sustainably improved the surgical results."

As mid-term to long-term ocular endotamponades (OEs), **perfluorocarbon gases** (as medical devices **hexafluoroethane & octafluoropropane**) have been established since the 1980s. After the surgical repair of retinal detachment or macular holes, the high interfacial tension of the perfluorocarbon gases enables the formation of an effective seal around retinal breaks and macular holes, respectively. Thus, it prevents the passage of intraocular fluid through the retinal breaks or macular hole, respectively, and restores the transretinal pressure gradient.
Considering the different postoperative OE agents, it is of importance to understand the differences in the above listed postoperative tamponade agents as they are not freely interchangeable. The tamponade agent is selected according to the requirements in relation to the severity of the managed vitreoretinal disease. **While air has a very short duration time in the vitreous cavity (5-7 days) and SF_6 is also considered as a short-term tamponade (duration 1-2 weeks)**, the perfluorocarbon gases C_2F_6 and C_3F_8 with durations in the vitreous cavity of 4-5 weeks and 6-8 weeks, respectively, represent mid-term and long-term tamponade agents, respectively (for duration times: Mohamed & Lai 2010). **Silicone oil (SO) tamponade is reserved to intended severe cases (which otherwise would suffer blindness) with respect to the numerous and partially serious side effects associated with its use as well as to the required second intervention for silicone oil removal and the complications associated with the modern retinal surgery as only in these cases the benefits of SO tamponade with special regard to the improvement or preservation of the visual acuity clearly outweigh the complications associated with its usage.**
The usage of **intravitreal air injections had become a standard procedure in the 1940s**. However, from the beginning on there was **dissatisfaction about the short residence time of the injected air bubble** and attempts were made to replace air with other gasses resulting in the introduction of SF_6 in 1973 (Norton) and of perfluorinated gases in the early 1980s (Lincoff A et al. 1980, Lincoff H et al. 1980, Lincoff et al. 1983, Lincoff et al. 1984). The indispensability of non-air gaseous OEs is exemplified once more by a recent publication of a prospective randomized noninferiority trial (Lindtjørn et al. 2022): In small and medium-sized macular holes, which represent relatively

uncomplicated conditions requiring generally only short-term endotamponation as provided by air or by SF_6, the trial proved that air tamponade is inferior to SF_6. In complicated cases requiring long-term OE, a recent randomized clinical trial concluded for silicone oil versus C_3F_8 gas tamponade with respect to a significantly better vision at 6 months (Rush et al. 2021; diabetic subjects with tractional retinal detachment or extensive fibrous proliferation): "**Vitreoretinal specialists should consider using C_3F_8 gas tamponade as the first-line vitreous substitute in this patient population.**" "There were no significant differences in baseline characteristics, intraoperative or postoperative complications, or incidence of unplanned PPV [*pars plana vitrectomies*] between groups."
Apart from their use as ocular endotamponade, C_2F_6 and C_3F_8 are used in pneumodescemetopexy, that is an intracameral (anterior chamber of the eye) injection of gas (SF_6, C_2F_6, C_3F_8) to achieve a mechanical tamponading action in the anterior chamber (eg. Chow et al. 2021, Ting & Srinivasan 2014, Kiire & Srinivasan 2009). Performed with air, multiple repeated injections are often required due to short resolution time and also with SF_6 repeated injections are required while with longer acting C_3F_8 a single injection was sufficient (Ting & Srinivasan 2014).

References

Abrams GE, Garcia-Valenzuela E, Nanda SK (2013). Chapter 108 - Retinotomies and Retinectomies. *In:* Ryan SJ, Hinton DR, Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann PW (eds) Retina, 5th Edition, Volume 3, pages 1826-1843. Saunders (an imprint of Elsevier Inc.). doi: 10.1016/B978-1-4557-0737-9.00108-9. *Retrieved via clinicalgate.com published 2015*

Berrocal MH, Chenworth ML, Acaba LA (2017) Management of Giant Retinal Tear Detachments. J Ophthalmic Vis Res. 12(1):93-97. doi: 10.4103/2008-322X.200158

Bourke RD (1995) Perfluorocarbon heavy liquids. Eye (Lond). 1995;9 (Pt 3):v-vii. doi: 10.1038/eye.1995.50

Bourke RD, Cooling RJ (1995) Perfluorocarbon heavy liquids. Aust N Z J Ophthalmol. 23(3):165-71. doi: 10.1111/j.1442-9071.1995.tb00151.x

Chow JY, Akhtar Ali AN, Bastion MC (2021) Pneumodescemetopexy With a Lower Concentration of Perfluoropropane (10% C3F8) in Descemet Membrane Detachment. Cureus 7;13(8):e16985. doi: 10.7759/cureus.16985

Feltgen N, Hoerauf H (2019) Aktueller Stellenwert von schweren Flüssigkeiten als intraoperative Hilfsmittel bei vitreoretinalen Eingriffen [Current importance of heavy fluids as intraoperative aids in vitreoretinal surgery]. Ophthalmologe. 2019 Oct;116(10):919-924. German. doi: 10.1007/s00347-019-0935-x

Hammer, M.E. (2016): AQUEOUS VITREOUS SUBSTITUTES, VISCOELASTIC SUBSTANCES AS VITREOUS, SUBSTITUTES, INTRAOCULAR GASES AS VITREOUS SUBSTITUTES, ABSORPTION AND KINETICS OF GASES INDICATIONS FOR INTRAOCULAR GASES, COMPLICATIONS OF INTRAOCULAR GASES AVAILABILITY OF GASES, SILICONE OIL AS A VITREOUS SUBSTITUTE, PERFLUOROCARBON LIQUIDS AS VITREOUS SUBSTITUTES, SEMIFLOURONINATED ALKANE LIQUIDS AS A VITREOUS SUBSTITUTE, http://www.oculist.net/downaton502/prof/ebook/duanes/pages/v6/v6c054.html

Kiire C, Srinivasan S (2009) Management of bilateral acute hydrops secondary to keratoglobus with perfluoroethane (C2F6) pneumodescemetopexy. Clin Exp Ophthalmol. 37(9):892-4. doi: 10.1111/j.1442-9071.2009.02160.x

Kohli P, Tripathy K. Agents for Vitreous Tamponade. 2023 Feb 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–

Lincoff A, Haft D, Liggett P, Reifer C (1980) Intravitreal expansion of perfluorocarbon bubbles. Arch Ophthalmol. 98:1646

Lincoff H, Coleman J, Kreissig I, Richard G, Chang S, Wilcox LM (1983) The perfluorocarbon gases in the treatment of retinal detachment. Ophthalmology 90:546-51

Lincoff H, Maisel JM, Lincoff A (1984) Intravitreal disappearance rates of four perfluorocarbon gases. Arch Ophthalmol. 102:928-9

Lincoff H, Mardirossian J, Lincoff A, Liggett P, Iwamoto T, Jakobiec F (1980) Intravitreal longevity of three perfluorocarbon gases. Arch Ophthalmol. 98:1610-1

Mohamed S, Lai TY (2010) Intraocular gas in vitreoretinal surgery. Hong Kong J Ophthalmol 14(1):8-13

Norton EW (1973) Intraocular gas in the management of selected retinal detachments. Trans Am Acad Ophthalmol Otolaryngol. 77:OP85-98

Regillo CD, Mahrous A (2021) Perfluorocarbon Liquids: Pearls and Pitfalls. Meeting Minutes ARDS - Retina Today January/February 2021

Rush RB, Del Valle Penella A, Reinauer RM, Rush SW, Bastar PG (2021) SILICONE OIL VERSUS PERFLUOROPROPANE GAS TAMPONADE DURING VITRECTOMY FOR TRACTIONAL RETINAL DETACHMENT OR FIBROUS PROLIFERATION: A Randomized Clinical Trial. Retina 1;41(7):1407-1415. doi: 10.1097/IAE.0000000000003052

Schulz A, Szurman P. (2022): Vitreous substitutes as drug release systems. Transl Vis Sci Technol. 2022;11(9):14, https://doi.org/10.1167/tvst.11.9.14

Ting DS, Srinivasan S (2014) Pneumodescemetopexy with perfluoroethane (C2F6) for the treatment of acute hydrops secondary to keratoconus. Eye (Lond). 28(7):847-51. doi: 10.1038/eye.2014.109

Wong D (2007). Slippage of the Retina: What Causes It and How Can It Be Prevented?. *In:* Kirchhof B, Wong D (eds) Vitreo-retinal Surgery. Essentials in Ophthalmology. Springer, Berlin, Heidelberg. doi: 10.1007/978-3-540-33670-9_4

Current Status of R&D for Alternatives

R&D efforts in the past 40 years had been performed. Driving forces were material costs, ecological considerations and improving material removal from the eye after surgery. Pharmpur itself was part of 3 major Research projects. All ended with failure of the investigated alternative materials as substitute of perfluorinated liquids for use in vitreoretinal surgery. There was also no lack of R&D activities from competitors and independent research organizations. However, no alternatives were identified. To date no promising candidate is being investigated nor in sight and the lack of success in the research for alternatives so far proves that identifying suitable alternatives is becoming more and more unlikely.

References

André Schulz, Karl T. Boden, Philip Wakili, Kai Januschowski, Werner R. Heinz, Melanie Engelhard, Helge Menz, Peter Szurman (2022): Evaluation von Hyaluronsäure-basierten Glaskörperersatzstoffen in Patienten mit Phthisis bulbi; 34th Annual Meeting of the German Retinological Society.

André Schulz, Anja Germann, Werner R. Heinz, Melanie Engelhard, Helge Menz, Annekatrin Rickmann, Ina Meiser, Sylvia Wagner, Hagen von Briesen, Kai Januschowski, Peter Szurman (2022): Hyaluronsäure-basierter Glaskörperersatz: Vom Labor zur Produktion; Ophthalmologie 119 (Suppl 3):S157–S344; https:// doi.org/ 10.1007/ s00347- 022- 01723-2

André Schulz, Philip Wakili, Kai Januschowski, Werner R. Heinz, Melanie Engelhard, Helge Menz, Peter Szurman (2023): Safety and performance assessment of hyaluronic acid-based vitreous substitutes in patients with phthisis bulbi; Acta Ophthalmologica; https://doi.org/10.1111/aos.15658

Specifically, the substances (perfluoroctane, perfluordecaline, C2F6, C3F8) are used because of their unique physical parameters as well as excellent biocompatibility since decades and during this time no substances suitable for alternatives have been found.

While aqueous vitreous substitution lacks the necessary mechanical and biochemical homeostasis of the eye, polymer-based hydrophilic vitreous substitutes have been proposed since many years as the native vitreous is a hydrogel composed of collagen fibres and hyaluronic acid. Additional to synthetic polymers, biopolymers have been investigated (e.g., hyaluronic acid or collagen, cross-linked hyaluronic acid and others). However, the investigated alternatives have been limited e.g., by degradation, insufficient biocompatibility or lack of transparency. Especially low substance purity or toxic cross-linking agents have hindered an implementation to clinical evaluation. As well, non-cross-linking polymer approaches failed for clinical application by degradation, lack of tamponading effect or short residence times. Pregelled hydrogels suffer from losing their rheological properties due to fragmentation induced by the injection via the state-of-the-art microinvasive cannulas used in vitreoretinal surgery (at least 23G, 25G is also already in use). As well, a variety of polymeric hydrogels are under evaluation in preclinical studies. (*Information extracted from: Schulz & Szurman 2022* ***as well as from Pharmpur's R&D department***).
To the best of our knowledge, no alternative substitute has entered the clinical phase of evaluation. Despite of recurring announcements of promising approaches in vitreous substitution, no

alternative will become available in the foreseeable future for replacement of perfluorocarbon ocular endotamponades.

In eye surgery these materials (perfluoroctane, perfluordecaline, C2F6, C3F8) have no alternatives. They are used for retinal eye surgeries as ocular endotamponades. If they will be banned or due to the ban within the PFAS regulation will not be available on the market anymore, patients will suffer blindness.

Reference:

Schulz A, Szurman P (2022) Vitreous Substitutes as Drug Release Systems. Transl Vis Sci Technol. 2022 Sep 1;11(9):14. doi: 10.1167/tvst.11.9.14

Impact of proposed Restriction on Patient Health and the Health System in the EU

Ocular endotamponades are indispensable in vitreoretinal surgery for preserving patients' vision. The perfluorinated materials are an integral part of the ocular endotamponade group, no adequate replacements are available in the foreseeable future despite many years of development, and, likewise, there do not exist adequate alternative treatments for the indication spectrum of perfluorinated ocular endotamponades. Remaining treatment options, as they were before the introduction of perfluorinated ocular endotamponades, result in extensive deterioration of the treatment outcome compared to the current state of the art with perfluorinated ocular endotamponades. This includes a distinct drop in functional outcome, which means ultimately blindness, based on a higher proportion on anatomical failure but especially based on inadequate management of the underlying diseases hindering cure or at least stopping of the disease or considerably lowering the course of the disease accompanied by a higher number of and/or more severe complications. If the perfluorinated ocular endotamponades are banned or become unavailable on the market due to the ban in the PFAS regulation, **a large proportion of patients with vitreoretinal disease will ultimately suffer blindness.**

Current Waste Management of the Products and Substances after Use

The medical devices produced at Pharmpur GmbH are offered in the volume needed for the corresponding operation. Therefore, there is no unnecessary waste due to leftovers during use.

Perfluorodecaline as well as perfluoroctane are removed from the eye at the end of the surgery, burned together with the clinical waste and fully destroyed according to Annex XV Restriction

Report, page 19, foot note 3: "Fully degrade implies mineralize to CO2, H2O and HF, leaving no persistent fluorinated organic metabolites that would fulfil the scope definition.".

These explants are classified as 18 01 03 according to the European Waste Catalogue (94/3/EC).

The standard procedure for this class of waste is the incineration of the hospital waste at temperatures of around 1,000° C, subsequent introduction of the combustion gases and the incineration residues into the domestic waste incineration boilers, and the filtering in a five-stage flue gas cleaning system to ensure the complete destruction of all organic compounds.

PFDeca: $C_{10}F_{18} + 9\ H_2O + 5.5\ O_2 \rightarrow 10\ CO_2 + 18\ HF$

PFOcta: $C_8F_{18} + 9\ H_2O + 3.5\ O_2 \rightarrow 8\ CO_2 + 18\ HF$

Both gasses, Hexafluoroethane and Perfluoropropane, are mid-term to long-term implants in the eye. They are not extracted from the eye but are transported through the blood system to the lung and exhaled within a defined time period (35 to 65 days).

Our Proposal for Reclassification of the Derogation of these Substances for Use as Ophthalmic Endotamponades (Medical Devices)

Based on the data and facts above (Assuming that alternative substances were available when the restriction came into force, they would then have to be approved as a new medical device. The following processes are necessary for this. Device design development, approx. 1 to 2 years; establishment and validation of production, approx. 1 to 2 years; stability studies, real time, 3 years; clinical trials, approx. 2 years; preparation of technical documentation, approx. 1 year; current times of testing at the notified bodies, on average at least 1.5 years; total in the best case scenario 9.5 to 11.5 years. However, since no alternative substance is currently available after decades of research and development, even the maximum period currently possible for a temporary derogation of 13.5 years, as described, is not sufficient) and due to the fact that these substances are **active substances** within the definition of medical devices, i.e. they are acting

physically acc. to their special chemical/physical properties, as well as even that a derogation period of 12 years is too short for the evaluation of alternatives (see above), we recommend that these **vital products** are listed in **RO2, paragraph 4 as a new clause d) for a derogation without time limit.**