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PREPARED FOR:

The European Chemicals Agency (ECHA) Scientific committees for Risk Assessment (RAC) and for Socio-Economic Analysis (SEAC)

PREPARED BY:

D.O.R.C. Dutch Ophthalmic Research Centre (International) B.V.

DATE:

22nd September, 2023

To Whom It May Concern,

Herewith D.O.R.C. Dutch Ophthalmic Research Center (International) B.V. writes to you in response to the PFAS restriction proposal dated March 22, 2023.

D.O.R.C. is a company that provides medical devices to ophthalmic surgeons that are intended to improve patients' vision and thus quality of life of patients. One of D.O.R.C.'s product types is ocular endotamponades (OE) which are based on per- and polyfluoroalkyl substances. The active substances in OE which are included within the scope of this comment are for perflunafen/perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), and perfluoropropane/octafluoropropane (C_3F_8). International standard EN ISO 16672 defines these substances as medical devices[1], however they are not currently listed for potential derogation within ECHA's restriction proposal in the use-case medical devices (Section A.3.10.1)[2] D.O.R.C. anticipates that the current proposal for restrictions will result in a ban on the use of PFAS-based OE.

However Retinal detachment (RD) is a medical emergency that requires prompt surgical intervention to preserve sight, functional ability, and quality of life.[3] If RD is not treated, permanent vision loss or blindness is inevitable.[4] PFAS-based OE play a critical role in the high success rate of today's retinal detachment surgeries, as evidenced by numerous clinical publications, which are listed at reference section.

Given the fact that Research & Development efforts in the past 40 years have not resulted in viable alternatives, D.O.R.C. strongly believes that 12 years derogation will be too short to introduce suitable alternatives to PFAS based OE.

In order for a device to be developed, the following steps are needed: approximately 1–2 years for device design; approximately 1–2 years to establish and validate production; approximately 2-3 years for stability studies; approximately 3-years for clinical trials; approximately 1 year for production of technical documents; and approximately 1.5 years for notified body review. In total, the best-case scenario is 13-14 years.[5]

Therefore, D.O.R.C. requests ***a new clause for a time-unlimited derogation and listing in the use 'medical devices'*** for perflunafen/perfluorodecalin (C10F18), perfluorooctane (C8F18), hexafluoroethane (C2F6), and perfluoropropane (C3F8).

In the following pages of this letter, we would like to provide you with additional information to show the necessity of the continued availability of PFAS based OE for patients.

We look forward to hearing from you in response.

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Substances in the scope of this comment :

EN ISO 16672 describes three classes of OE: 1) gaseous 2) perfluorocarbon liquids (PFCLs) and 3) silicone oils.[1] The active substances in OE that are impacted by the proposed restriction on the manufacture, placing on the market and use of PFASs and included within the scope of this comment are listed in below.

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

General	
INN	Perfluoroctane
Synonyms	Octadecafluoroctan 1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Octadecafluoroctan
Molecular Formula	C_8F_{18}
CAS Registry Number	
CAS	307-34-6
Molecular Mass	438.06 $g \cdot mol^{-1}$

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

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

Production and Sales Data

D.O.R.C. has delivered 55.405 units of PFAS based OE to the global ophthalmic market in 2022. According to D.O.R.C.`s annual financial report, 61% of total units generated in European market.[6]

In totally, annual production within European market from D.O.R.C. is 404.7 kg.[7]

- Perfluorodecalin = 275 kg
- Perfluoroctane = 121 kg
- Perfluoropropane = 5.2 kg
- Hexafluoroethane = 3.5 kg

ECHA has reported that total emissions of PFAS substances is 75.000 tonnes in 2020. This means only 0,0005% of total emission comes from ophthalmic products produced by D.O.R.C.

Users of these substances are Healthcare Professionals in public and private hospitals, clinics, and ambulatory eye centres who conduct vitreoretinal surgeries.

History, application and clinical background of Ocular Endotamponades

OE are non-solid surgically invasive medical devices introduced into the vitreous cavity of the eye to flatten and position a detached retina onto the RPE, or to tamponade the retina.
EN ISO 16672 describes three classes of OE: 1) gaseous OE; 2) PFCLs; and 3) silicone oils.[1]

OE can be used intraoperatively and removed at the end of surgery (i.e. PFCLs), remain in the vitreous cavity and removed later (i.e. silicone oils), or they are reabsorbed via passive diffusion (i.e. gaseous OE).[8] The choice of OE depends upon the severity and location of the retinal detachment, patient characteristics, tamponade duration, and the specific risk–benefit profile.[9]

PFCLs :

As an intraoperative tool in vitreoretinal surgery, PFCLs have been established since the 1980s for the hydrokinetic manipulation of the detached neurosensory retina. Currently, there are no PFAS-free alternatives to PFCLs. PFCLs are used especially in complicated retinal detachments where the neurosensory retina may be completely detached, folded or even be in a funnel-shaped configuration 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 stabilizes the retina during procedures for removal of tractions to the retina posed by pathological membranes.[10] 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[11] and retinal tacks had to be used to fix the retina to the wall of the eye mechanically. [12]

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Prior to the use of PFCLs, retinal reattachment was achieved by fluid-air exchange only. However with a few exceptions, this technic was required 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 located 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 traction on the anterior retina.[13] This traction may result in the following situations[13] :

1. Stretching of the retina resulting in limited macular translocation
2. Folding of the retina – iatrogenic retinal folds – often passing through macula and it causes reduction of visual acuity and often are accompanied by disturbing symptoms of distortion
3. Slippage of the retina

Posterior drainage retinotomy can be associated with significant complications, including hemorrhage, fibrosis with traction, choroidal neovascularization, and visual field loss.[14] In contrast to air, PFCL replaces the subretinal fluid anteriorly and can thereby avoid the need for posterior drainage retinotomy. 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.[15] PFCL minimizes macular distortion or folds.[16]

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.[15]

Further indispensable intraoperative applications of PFCLs are[11]:

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 properties, in particular non-metallic IOFBs rely on mechanical removal.
2. In ocular trauma, 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[17] :

“Heavy fluids have become an indispensable intraoperative aid in vitreoretinal surgery and have sustainably improved the surgical results.”

Gaseous OE :

As mid-term to long-term gaseous OE have been established since the 1980s. After the surgical repair of retinal detachment or macular holes, the high interfacial tension of gaseous OE 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, it is important to understand the differences between PFAS based OE and PFAS-free OE as they are not freely interchangeable. Each OE should be selected according to the requirements in relation to the severity of the managed vitreoretinal disease.

- ***PFAS-based gaseous OE*** have 4-8 weeks durations in the vitreous cavity.[18]
- ***Air (PFAS-free OE)*** has a very short duration time in the vitreous cavity (5-7 days). [18] The usage of intravitreal air injections had become a standard procedure in the 1940s. However, since then there is dissatisfaction about the short residence time of the injected air bubble. It led the ophthalmic society to replace the air with gaseous OE such as introduction of SF6 in 1973 and of PFAS-based gaseous OE in the early 1980s.[19-22]
- **SF_6** ***(PFAS-free gaseous OE)*** is also considered as a short-term tamponade with 1-2 weeks duration. [18] The indispensability of non-air gaseous OE is exemplified once more by a recent publication of a prospective randomized non-inferiority trial. 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 requires long-term OE, a recent randomized clinical trial concluded for silicone oil versus C_3F_8 (PFAS-based gaseous OE) with respect to a significantly better vision at 6 months.[23] The article recommends that `Vitreoretinal specialists should consider using $C_3F_8$ gas tamponade as the first-line vitreous substitute in this patient population. `
- ***Silicone oil (PFAS-free OE)*** 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. Also it requires a second intervention for silicone oil removal. The complications associated with the modern retinal surgery as only in these cases the benefits of silicon oil with special regard to the improvement or preservation of the visual acuity clearly outweigh the complications associated with its usage. Unlike gases, the silicone oil tamponade does not re-absorb naturally but instead must be removed by a second surgery.

Additionally, PFAS based gaseous OE 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.[24] 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.[25-26]

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Current Waste Management of PFAS based OE after use

The medical devices marketed by D.O.R.C. are offered in the volume needed for the corresponding operation. Therefore, there is no unnecessary waste due to leftovers during use.

PFCLs should be 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: $C_{10}F_{18} + 9\ H_2O + 5.5\ O_2 \dashrightarrow 10\ CO_2 + 18\ HF$

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

PFAS based gaseous OE 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).

Current Status of Research & Development for PFAS – free Alternatives

Multiple R&D efforts had been performed in the past. PFAS based OE used for decades thanks to its unique physical parameters and excellent biocompatibility. There are significant challenges associated with developing a suitable vitreous substitute. 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 fibers 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 due to degradation, insufficient biocompatibility or lack of transparency. Especially low substance purity or toxic cross-linking agents have hindered an implementation into clinical practice. Also, non-cross-linking polymer approaches failed for clinical application by degradation, lack of tamponading effect or short residence times.

Pre-gelled hydrogels suffer from losing its 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). Also, a variety of polymeric hydrogels are under evaluation in preclinical studies.[27]

Therefore, there is no suitable 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 PFAS based OE.

Accordingly, alternative substances should be approved as a new medical device before the market introduction. Presently, new medical device approval is lengthy process which needs to apply the following timeframe :

- Device design development - *approx. 1 to 2 years*
- Validation and establishment of production - *approx. 1 to 2 years*
- Stability studies, real world evidence generation – *3 years*
- Clinical trials - *approx. 2 years*
- Technical documentation – *1 year*
- Testing at Notified Bodies –*1.5 years*

This means that new research & development activities are highly unlikely to lead to a change in global clinical practice within the 5-year and 12-year derogation periods.

Total number of patients treated with PFAS based OE

According to an internationally recognized marketing report for the ophthalmic community[1], retina surgeons use ocular gaseous tamponades in 49.5 percent of vitreoretinal surgical procedures. An estimated 10 percent of vitrectomy procedures in the developed countries involve the use of perfluorocarbon liquids (PFCLs) to seal retinal breaks and detachments.

Globally, it is estimated that in 2023, about 926 thousand patients will be operated with the assistance of PFAS based OE with an estimated 27% of patients in the Western Europe countries.

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

OE are indispensable in vitreoretinal surgery for preserving patients' vision. The perfluorinated compounds are an integral part of the OE group. Consequently, the withdrawal of PFAS containing OE would create a significant clinical unmet need. This is a high risk of the proposed restriction option to patient-outcomes, direct medical costs, and indirect costs. It is indicative of a serious patient level impact, and increased economic burden to impacted individuals and caregivers, the healthcare systems and EU societies because of the proposed restriction.

Few PFAS-free alternatives are under investigation however the timeline for their clinical developments and certifications mean that they will not be available at the entry into force date and will highly unlikely be available within the 5-year and 12-year derogation periods.

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Remaining treatment options, as they were before the introduction of PFA based OE, result in extensive deterioration of the treatment outcome compared to the current state of the art with PFA based OE. This includes a distinct drop in functional outcome, which ultimately results in impaired vision and blindness.

Additionally, the inadequate management of the underlying diseases will hinder the cure or the stabilization of the disease which will result in an increase of the occurrence and severity of the complications. If PFA based OE will be 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 severe impaired vision and even blindness.

Request to ECHA

D.O.R.C. Dutch Ophthalmic Research Centre (International) B.V. requests a time-unlimited derogation and listing in the use 'Medical devices' (Section A.3.10.1) for perflunafen/perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), and perfluoropropane/octafluoropropane (C_3F_8).

Your sincerely,

Pierre Billardon

DocuSigned by:
Pierre Billardon
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Chief Executive Officer

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