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Response to the European Chemicals Agency (ECHA) restriction on the manufacture, placing on the market, and use of per- and polyfluoroalkyl substances (PFASs)

Comments for Annex XV restriction report

Report v2.0

CONFIDENTIAL

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PREPARED FOR:

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

DATE:

22nd September 2023

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ABBREVIATIONS

$C_{10}F_{18}$	Perflunafen (perfluorodecalin)
C_2F_6	Perfluoroethane
C_3F_8	Perfluoropropane
C_8F_{18}	Perfluoro-n-octane
CAS	Chemical Abstracts Service
CO_2	Carbon dioxide
ECHA	European Chemicals Agency
EU	European Union
EURETINA	European Society of Retina Specialists
F_6H_8	Perfluorohexyloctane
H_2	Hydrogen
HCRU	Healthcare resource use
INN	International non-proprietary name
ISO	International Organization for Standardization
NSR	Neurosensory retina
OE	Ocular endotamponades
PDMS	Polydimethylsiloxane polymers
PDR	Proliferative diabetic retinopathy
PFAS	Per- and polyfluoroalkyl substance
PFCL	Perfluorocarbon liquids
PFD	Perfluorodecalin
PFO	Perfluorooctane

PVD	Posterior vitreous detachment
RAC	Scientific committees for Risk Assessment
RD	Retinal detachment
RO1	Restriction option 1
RO2	Restriction option 2
RPE	Retinal pigment epithelium
RRD	Rhegmatogenous retinal detachment
SF_6	Sulphur hexafluoride
TLR	Targeted literature review
TRD	Tractional retinal detachment
TRRD	Combined traction-rhegmatogenous retinal detachment

EXECUTIVE SUMMARY

Introduction: A group of industry stakeholders have collaborated to conduct an independent study in response to the European Chemicals Agency (ECHA) restriction proposal on the manufacture, placing on the market, and use of per- and polyfluoroalkyl substances (PFASs). The industry stakeholder group comprises of Alchimia S.r.L, Bausch & Lomb, BVI, Carl Zeiss Meditec, D.O.R.C. Dutch Ophthalmic Research Centre (International) B.V. and Pharmpur GmbH. Each company within the industry stakeholders manufacture ocular endotamponades (OE) that are used in vitreoretinal surgery. The active substances in OE which are included within the scope of this comment are perflunafen/perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), perfluorohexyloctane (F_6H_8), perfluoropropane (C_3F_8), and heavy silicone oil. 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] The objective of this study was to demonstrate the application of OE in the surgical management of retinal detachment (RD), and to conduct a prospective risk-impact assessment on patient outcomes, direct medical costs, and indirect costs associated with the proposed restriction options. Additionally, the study will evaluate the availability of technically and economically feasible alternatives.

Methodology: An independent healthcare consultancy was commissioned to conduct the research.[3] The study combined a targeted literature review (TLR) and a survey with a panel of vitreoretinal surgeons in France, Germany, Italy, Spain, and the Netherlands. The TLR covered three domains: 1) the humanistic and economic burden of RD; 2) clinical guidelines on the role of OE in the surgical management of RD; and 3) availability of technically and economically feasible alternatives. The survey included six sections: 1) consent to participate; 2) introduction and objectives; 3) about you; 4) role of OE in the surgical management of RD; 5) prospective risk-impact assessment; and 6) recommended response to ECHA.

Results and discussion: RD is a medical emergency that requires prompt surgical intervention to preserve sight, functional ability, and quality of life.[4] If RD is not treated, permanent vision loss or blindness is inevitable.[5] OE have a long history and critical role in the surgical management of RD. There are three categories of OE: 1) gases (air, SF_6, C_2F_6, C_3F_8); 2) perfluorocarbon liquids (PFCLs); (C_8F_{18}, $C_{10}F_{18}$, F_6H_8); and 3) silicone oils (heavy and conventional). All categories are used in the main surgical interventions which include pars plana vitrectomy, scleral buckle and pneumatic retinopexy.[19-35] The choice of OE depends upon the severity and location of the retinal detachment, patient characteristics, tamponade duration, and the specific risk-benefit profile.[6] Regulatory approved PFAS-free OE exist (air, SF_6 and conventional silicone oil), but they are associated with limitations and are not suitable for all clinical contexts. PFAS-free OE are only suitable for the treatment of ~19% of RD patients, leaving the potential for 81% of patients to be untreatable if PFAS-containing OE were removed from the market.[7] Consequently, the withdrawal of PFAS containing OE would create a significant clinical unmet need. The prospective risk-impact assessment demonstrated the high risk of the proposed restriction option to patient-outcomes, direct medical costs, and indirect costs. This 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. These investigations are in the early stages, in small cohorts (n=10–50), and in a small number of centres, including non-European locations and will in all likelihood take more than 12 years to be developed for safe use in patients. This

means that they are highly unlikely to lead to a change in global clinical practice. Consequently, 81% of the panel supported a time-unlimited derogation for this use-case.

Conclusion: This study has demonstrated the critical role of PFAS-containing OE in the surgical management of RD. Withdrawal of the substances in the scope of this comment will result in over 80% of RD cases being surgically untreatable, with the devastating consequence of vision impairment, blindness, and other visual complications in otherwise surgically treatable eyes. The proposed restriction would result in a substantial and negative impact on patient outcomes, direct medical costs, and indirect costs. PFAS-free options exist, but they are associated with limitations in clinical practice. OE manufacturers will not be able to replace these substances by the entry-into-force date, nor by the 5-year or 12-year derogation periods.

Request to ECHA: The industry stakeholder group request a new clause for a time-unlimited derogation and listing in the use 'medical devices' for perflunafen/perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), perfluorohexyloctane (F_6H_8), perfluoropropane (C_3F_8), and heavy silicone oil.

1.0 INTRODUCTION

A group of industry stakeholders have collaborated to conduct an independent targeted literature review (TLR) and primary research study in response to the European Chemicals Agency (ECHA) restriction proposal on the manufacture, placing on the market and use of per- and polyfluoroalkyl substances (PFASs). Mtech Access is an independent and impartial healthcare consultancy commissioned to conduct the research.[3] The industry stakeholders comprises of Alchimia S.r.L, Bausch & Lomb, BVI, Carl Zeiss Meditec, D.O.R.C. Dutch Ophthalmic Research Centre International B.V. and Pharmpur GmbH.

1.1 Background

Each company within the industry stakeholder group manufactures ocular endotamponades (OE) that are used in vitreoretinal surgery. OE are defined in international standard EN ISO 16672 as 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.[1] EN ISO 16672 describes three classes of OE: 1) gaseous 2) perfluorocarbon liquids (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 be removed later (i.e. silicone oils), or they are reabsorbed via passive diffusion (i.e. gaseous OE).[10] Users of these substances are Healthcare Professionals in public and private hospitals, clinics, and ambulatory eye centres who conduct vitreoretinal surgeries.

1.2 Substances in the scope of this comment

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 Appendix 1. They include perflunafen/ perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), perfluorohexyloctane (F_6H_8), perfluoropropane (C_3F_8), and heavy silicone oil. The active substances listed above are defined by EN ISO 16672 as medical devices;[1] however, they are not listed within ECHA's restriction proposal in Section A.3.10.1. Medical devices.[2] Therefore, the industry stakeholders have recommended listing these substances within the 'Medical devices' section.

1.3 Objectives

This study was commissioned by the industry stakeholders to demonstrate the application of OE in the surgical management of retinal detachment (RD) and to conduct a prospective risk-impact assessment of the proposed restriction options on patient outcomes, direct costs, and indirect costs. Additionally, the study assessed the availability of technically and economically feasible alternatives.

2.0 METHODOLOGY

An independent healthcare consultancy was commissioned to conduct the research.[3] A TLR was conducted to establish the application of OE in the surgical management of RD. The review focused on three areas:

1. The humanistic and economic burden of RD
2. The types of surgical intervention and the role of different regulatory approved OE in the surgical management of RD
3. An assessment of the availability of technically and economically feasible alternatives

A survey was conducted with a panel of vitreoretinal surgeons to gather expert opinions on the role and importance of OE in the surgical management of RD and to conduct a prospective impact assessment of the proposed restriction options on patient outcomes, direct costs, and indirect costs.

2.1 Targeted literature review

2.1.1 Overview

The scope of the TLR included five European markets: France, Germany, Italy, Spain, and the Netherlands. The review covered three domains:

- **Burden of disease:** To understand the pathology and pathogenesis of RD and the humanistic and economic burden of the disease
- **Clinical guidelines:** To establish the current clinical consensus on the surgical management of RD, and the role of OE in the care pathway
- **Availability of technically and economically feasible alternatives:** To identify the current regulatory approved OE and their chemical and physical properties and to evaluate the research and development pipeline to identify any PFAS-free alternatives in development

2.1.2 Search parameters

2.1.2.1 Burden of disease

To explore the burden of RD, a PubMed search of published, peer-reviewed research studies was conducted. Search terms are provided in Table 1.

Table 1: Burden of disease – Search terms

Topic	Search term	
Disease	Retinal detachment	Exudative
	Rhegmatogenous	Retinal tear
	Tractional	Retinal hole
Impact	Incidence	Comorbidity
	Prevalence	Quality of life
	Frequency	Activity
	Mortality	Socio-economic
	Complications	Productivity
	Cost	Humanistic
	Burden	Economic

2.1.2.2 Clinical guidelines

A targeted search of professional medical society websites was conducted to identify published evidence-based guidelines for the surgical management of RD. Sources are provided in Table 2.

Table 2: Professional medical society websites

Country	Source	Website
France	Société Francaise Ophtalmologie/French Society of Ophthalmology	*www.sfo.asso.fr/*
Germany	Deutsche Ophthalmologische Gesellschaft/German Ophthalmological Society	*www.dog.org/*
	Bundesverband für Ambulantes Operieren e.V./Federal Association for Outpatient Surgery	*www.operieren.de/*
Italy	Società Oftalmologica Italiana/Italian Ophthalmological Society	*www.soiweb.com/*
	Gruppo Italiano di Chirurgia Vitreoretinica/Italian Group of Vitreoretinal Surgery	*www.givre.it/*
Spain	Socieded Espanola De Oftalmologia/Spanish Society of Ophthalmology	*www.oftalmoseo.com/*
The Netherlands	Nederlands Oogheelkundig Gezelschap /Ophthalmological Society of the Netherlands	*www.oogheelkunde.org/*
Europe	European Society of Retina Specialists (EURETINA)	*www.euretina.org/*
	European Society of Ophthalmology	*www.soevision.org/*

Additional searches were conducted using Google and Google Scholar. Google translate was used to conduct the searches in French, German, Dutch, Spanish and Italian. Search terms are provided in Table 3.

Table 3: Clinical guidelines – Search terms

Topic	Search terms

Surgical technique	Ocular tamponade(s); endotamponade(s) Pneumatic retinopexy Pars plana vitrectomy; vitrectomy	Scleral buckle; scleral buckling; scleral indentation; scleral depression Surgery; surgical; operative
Disease	Retinal detachment Rhegmatogenous Tractional	Exudative Retinal tear Retinal hole
Tamponades	Gas Air Sulphur hexafluoride; SF_6 Hexafluoroethane; perfluoroethane; C_2F_6 Perfluoropropane; C_3F_8 Silicone oil; heavy; conventional	Perfluorocarbon liquids (PFCL) Perfluoroctane; C_8F_{18} Perfluorohexyloctane; F_6H_8 Perflunafen; perfluorodecalin; $C_{10}F_{18}$ PFAS; per- and polyfluoroalkyl
Guidelines	Guideline(s); guidance Position statement Consensus	Clinical Pathway Management; treatment

2.1.2.3 Availability of technically and economically feasible alternatives

2.1.2.3.1 Regulatory approved OE

EN ISO 16672 was used to produce a list of current regulatory approved OE.[1] PubMed and Google Scholar searches were used to obtain information on the chemical and physical properties associated with each OE.

2.1.2.3.2 Research and development pipeline

A targeted search of the Clinicaltrials.gov database was conducted to identify clinical trials to investigate OE for the treatment of RD. Search terms and filters are described in Table 4.

Table 4: Clinicaltrials.gov – Search terms and filters

Category	Search term or filter
Condition or disease	Retinal detachment and its synonyms Ocular tamponade; endotamponade
Intervention or treatment	Include drug, medical device, procedure, other Exclude vaccine, diagnostic test and studies relating to regulatory approved OE
Location	No filter
Study status	No filter
Eligibility criteria	No filter
Study phase	No filter
Study type	No filter
Date range	01/01/2013 – 01/09/2023

Abbreviations: OE, ocular endotamponades.

Additionally, PubMed and Google scholar were searched to identify recent publications relating to future advancements in the surgical management of RD.

2.2 Primary research survey

2.2.1 Overview

Although the scope of the ECHA proposal will apply to all EU countries, the primary research survey was conducted in a sub-set of five European markets (France, Germany, Spain, Italy, and the Netherlands) to permit data collection and international co-ordination and to allow a time-sensitive response. The purpose was to gain expert opinions on the role of OE in the surgical management of RD and to conduct a prospective impact assessment of the proposed restriction options.

2.2.1.1 Sample/recruitment

The survey aimed to recruit an expert panel of up to 20 ophthalmologists with experience in vitreoretinal surgery (n=4 in each country, France, Germany, Spain, Italy, and the Netherlands). Respondents were identified by the industry stakeholders as a group of key opinion leaders and influential experts in this indication, with many holding senior positions in professional medical societies. Respondents were invited to participate via email. Data collection was conducted between 25th August and 10th September 2023.

2.2.1.2 Survey design

The survey was developed in an online digital format and comprised of six sections:

- **Consent to participate:** To present essential information relating to market research codes of conduct and to gather consent to participate
- **Introduction and objectives:** To present information on what PFAS are and why ECHA is concerned about the negative effects on human health and the environment. Additionally, to present detail of the proposed restriction options, transition period, and derogations

- **About you:** To collect basic demographic information on the professional experience of respondents in relation to vitreoretinal surgery
- **Role of OE in the surgical management of RD:** To validate the outputs of the targeted literature review with respect to the surgical management of RD and to gain the experts' perspective on the role and importance of different OE
- **Prospective impact assessment:** To gain the expert panel's predictions for the impact of the proposed restriction options on patient outcomes, direct medical costs, and indirect costs
- **Conclusion:** To gather the expert panel's recommendations in response to the proposed restriction options, transition period and derogations

A mixture of open-ended and closed-ended questions were used. The closed-ended questions included multiple choice (single or multiple response format) and continuous 5-point Likert rating scales. Open-ended questions were used to provide qualitative and contextual insights.

2.2.1.3 Analysis

Data were extracted from the survey and imported into an Excel spreadsheet for analysis. Descriptive statistics including mean, and range were applied to the continuous 5-point Likert scales. Frequency counts were applied to the single and multiple-choice responses. To create the prospective risk-impact matrices, the mean impact was calculated for each criterion and plotted on the X axis (ranging from 1 [no impact] to 5 [severe impact]), and the mean likelihood was calculated and plotted on the Y axis (ranging from 1 [not at all likely] to 5 [extremely likely]). This enabled visualisation of the overall risk of each variable, considering its impact and likelihood.

3.0 RESULTS

3.1 Targeted literature review

3.1.1 Burden of RD

Retinal detachment (RD) is the separation of the neurosensory retina (NSR) from the underlying retinal pigment epithelium (RPE).[11] RD is a sight-threatening condition and is considered one of the few known ocular emergencies.[11] The retina is one of the most metabolically active tissues in the body. When the retina detaches from the underlying RPE, it loses oxygen and nutrient supply, resulting in retinal ischaemia.[4, 12] Without surgical intervention, retinal detachment can lead to permanent blindness in the affected eye. Therefore, prompt diagnosis and treatment are critical to prevent visual loss, functional impairment and maintain quality of life.[4]

Retinal detachment occurs when subretinal fluid accumulates between the NSR and the RPE. This process can occur through different mechanisms, resulting in four major types of RD: rhegmatogenous, tractional, exudative, and combined tractional-rhegmatogenous.[11]

Rhegmatogenous retinal detachment

Rhegmatogenous retinal detachment (RRD) is the most common form of RD and is characterised by the presence of a full thickness retinal break or defect in the NSR.[11, 13] This allows fluid from the vitreous cavity to enter the subretinal space, resulting in the separation of the NSR from the underlying RPE.[13] In order for

an RRD to occur, the vitreous must be at least partially liquefied, as this provides the low viscosity fluid that is able to flow through the retinal break.[11] Predisposing factors to RRD are less obvious than for the remaining types of retinal detachment – they include vitreoretinal adhesions in association with posterior vitreous detachment (PVD), local ocular diseases, cataract surgery and trauma.[11]

Previously untreatable, RRD now achieves primary surgical success rates of over 80–90%, with complex cases also being amenable to treatment.[13]

A meta-analysis conducted in 2019 found the mean annual incidence of RRD in Europe to be 13.3 cases per 100,000 inhabitants.[14]

Tractional retinal detachment

Tractional retinal detachment (TRD) occurs when the NSR separates from the RPE due to tractional forces in the absence of a retinal tear.[11] This type of retinal detachment is most common in proliferative retinal and vitreoretinal diseases, the most common being proliferative diabetic retinopathy (PDR), which is a complication of prolonged and uncontrolled diabetes mellitus.[11, 15]

Due to the multifactorial aetiology of TRD, the exact epidemiology has not been reported in large scale studies.[16]

Exudative retinal detachment

Exudative retinal detachment occurs when there is a disruption to the integrity of the blood-retinal barrier, leading to accumulation of fluid from the vessels of the retina, the choroid, or both.[17] This can occur in a number of vascular, inflammatory and neoplastic diseases of the retina, RPE and choroid.[11] This type of retinal detachment can also occur due to accumulation of blood in the subretinal space, known as haemorrhagic retinal detachment.[11]

Due to the multifactorial origin of exudative retinal detachment, no previous data on the frequency of the disease were available in reviewing the literature.[18]

Combined traction-rhegmatogenous retinal detachment

Combined traction-rhegmatogenous retinal detachment (TRRD) occurs because of a combination of a retinal tear and retinal traction. The major component of retinal detachment is usually traction with the tear being the secondary mechanism. TRRD is therefore also most common in proliferative retinal and vitreoretinal diseases.[11]

3.1.2 Surgical management of RD

Guidelines from professional medical societies listed in Table 2 describe the current medical consensus for the surgical management of RD. A summary of the three main surgical techniques, pars plana vitrectomy, scleral buckle and pneumatic retinopexy, is presented in Figure 1.[19-35]

3.1.2.1 OE: their role, and chemical and physical properties

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.[1] 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).[10] The choice of OE depends upon the severity and location of the retinal detachment, patient characteristics, tamponade duration, and the specific risk–benefit profile.[6] The chemical and physical properties of each of the categories of OE is presented in Table 5 and Table 6.

3.1.2.1.1 PFCLs

PFCLs are a group of dense liquids that are used during surgery to reattach the retina and are mainly used during complex cases. PFCLs do not remain in the eye and are removed at the end of surgery. PFCLs are crucial in the manipulation and flattening of the retina, and greatly improve the efficiency and safety of these procedures.[36]

3.1.2.1.2 Gaseous OE

Gas tamponades are used during most types of RD surgery (e.g. pars plana vitrectomy, scleral buckling and pneumoretinopexy). The gas is injected into the eye during surgery to flatten the retinal break. The gas is left in the eye to be gradually reabsorbed, in contrast to silicone oils, which require a second surgery to remove.[39] The most commonly used gas tamponades are C_3F_8 and SF_6, which have been the standard of care since the 1990s.[37, 38] C_3F_8 remains in the eye for approximately 8 weeks and is categorised as a Class IIb medical device based on this long-term retention in the eye.[1] In contrast, SF_6 is retained in the eye for approximately 2 weeks and is categorised as a Class IIa medical device based on its shorter-term retention in the eye.[1]

3.1.2.1.3 Silicone oils

Silicone oils are used as longer-term tamponade agents and are suitable in clinical cases when the tamponade must remain in place for a longer period of time to promote retinal reattachment. Indications for the use of silicone oil include more complex cases, such as RRD with proliferative vitreoretinopathy.[39] Unlike gases, the silicone oil tamponade does not re-absorb naturally but instead must be removed by a second surgery.[39]

3.1.2.1.4 PFAS containing OEs

Within the three main categories of OE (PFCLs, ocular gases, and silicone oils), ocular gases and silicone oils can be further categorised into PFAS-containing and PFAS-free.

PFCLs are fluorochemicals, and their unique chemical composition is what makes them an ideal interoperative tool.[40] However, all PFCLs contain PFAS (C_8F_{18}, $C_{10}F_{18}$, and F_6H_8) so are therefore impacted by the proposed restriction by ECHA. There are no PFAS-free alternatives to PFCLs.

Gas tamponades include air and SF_6 which are PFAS-free, and C_2F_6 and C_3F_8 which are PFAS-containing. The main differentiator of the different types of gaseous OE are the length of duration in the eye, and the surgeon's choice depends on the desired length of the tamponade effect. Air has the shortest tamponade duration of 5-7 days, and C_3F_8 has the longest duration of up to 8 weeks (Table 5).

There are two categories of silicone oil tamponades: conventional, which is PFAS-free; or heavy silicone oil, which is conventional silicone oil plus semi fluorinated alkanes, which are PFAS-containing (Table 5). The two categories differ in that heavy silicone oil has a higher density so is favoured for its ability to treat

inferior RDs, and is useful in patients that cannot perform post-operative posturing, which conventional silicone oil is not appropriate for.[41]

Figure 1: Surgical management of retinal detachment

Diagnosis, assessment, and referral for surgery

Only surgery can prevent loss of vision following retinal detachment, and cross-country guidance highlights the importance of timely surgical intervention to preserve sight.[19,20] Retinal detachment is assessed via eye examinations, visual acuity tests, ophthalmoscopy, or ocular ultrasound.[21,22,23] It is important to determine the location of the tear and type of pathology, as this informs the subsequent course of action[22]. The three main types of retinal pathology are rhegmatogenous, tractional, and exudative. Both tractional and rhegmatogenous retinal detachment require surgery, but not exudative.[35]

Surgical management

There are three main procedures used in the surgical management of retinal detachment – pars plana vitrectomy, scleral buckling and pneumatic retinopexy. All three may use an ocular endotamponade (silicone oil, gas, or perfluorocarbon liquids/semi fluorinated alkanes). The choice of tamponade is not standardised or specified in ophthalmological guidelines in the five countries and depends on the clinical need and severity of the detachment. The choice of procedure also depends on severity of detachment, macular involvement and vitreoretinal proliferation.[24,25]

Pars plana vitrectomy

The vitreous is removed and the retinal break is closed using laser or cryotherapy. Based on the characteristics of the detachment, a buffering substance is used to replace the vitreous fluid and hold the retina in place: either SF_6 or C_3F_8 gas or silicone oil. Silicone oil requires another operation to remove, whereas gas is reabsorbed on its own.[19,20,25,26,27] In cases where the risk of recurrence is high, the buffering substance will not be removed.[20]

Scleral buckle

A grooved buckle is placed at the level of the tear, creating an indentation in the eye wall that causes the underlying choroid to press against the retina and close the tear. The retinal tear can be closed with laser photocoagulation or cryotherapy. In some cases, the fluid is drained from the eye and gas or air is injected into the vitreous cavity for stronger adhesion.[19,20,25,19,26,27]

Pneumatic retinopexy

In the case of retinal ruptures located in the upper two thirds of the fundus, a pneumatic retinopexy is performed where a gas bubble is injected into the vitreous cavity, usually C_3F_8 or SF_6. Laser photocoagulation is used to repair the break. Pneumatic retinopexy is typically used for 'uncomplicated' retinal detachments.[20,25,26,28] Pneumatic retinopexy is used less frequently in France[19] and used to treat smaller tears in Germany.[21]

Pars plana vitrectomy is the most widely used option for complex and recurrent retinal detachment.[30,31]
Scleral buckling is commonly used for uncomplicated retinal detachment or where the patient's natural lens is still in place (as opposed to an artificial lens placed during cataract surgery), but its popularity has declined in recent years.[32]
Pneumatic retinopexy is used less frequently than pars plana vitrectomy and scleral buckling, but is favoured as a minimally invasive and non-incisional procedure with faster recovery times.[33]

Postoperative care

Further surgery may be required to remove the silicone oil tamponade. Patients are instructed to apply antibiotic/anti-inflammatory eye drops, ointment and a protective covering to the eye. Patients should limit usual activities to prevent eye strain and keep their head in a certain position for a specific period of time.[19,23,26,27,34]

In Germany and the Netherlands, the choice of vitrectomy or scleral buckle depends on if patient has previously had cataract surgery and an artificial lens fitted

In German and Italian guidelines, laser and cryocoagulation techniques are used in cases of an incomplete rupture and can be completed in the outpatient setting. Laser or cryotherapy on its own is reserved for less severe cases and generally do not use PFAS containing products[21, 29]

Table 5: Ocular endotamponades and their chemical/physical properties

	Chemical formula	PFAS-containing/ impacted by ECHA restriction	Duration in the eye	100% gas expansivity	Isoexpansile concentration	Injection times	Viscosity (cSt)	Interfacial tension (mN/m)
Conventional silicone oil[36, 42]	Conventional silicone oil (PDMS)	✗	Long-term, requires surgical removal to restore clear vision and prevent negative outcomes	-	-	50–240 seconds	1,000–5,000	35
Heavy silicone oil[6, 36, 42-44]	Conventional silicone oil + partially fluorinated C_nH_{2n}/C_nH_{2n+2} (PDMS + partially fluorinated alkene/ alkane)	✓		-	-	N/A	1,400–3,300	41–45
Gas tamponade[6, 36, 42-44]	Air	✗	5–7 days	-	-	-	-	70
	SF_6 (sulphur hexafluoride)	✗	2 weeks	2x	20%	-	-	70
	C_2F_6 (perfluoroethane)	✓	4–5 weeks	3x	16%	-	-	70
	C_3F_8 (perfluoropropane)	✓	8 weeks	4x	14%	-	-	70
PFCL/semi fluorinated alkanes[36, 42, 45-49]	C_8F_{18} (perfluoro-n-octane)	✓	Short-term, as an intra-operative aid Short/medium term as a post-operative tamponade†	-	-	-	0.8	55.0
	$C_{10}F_{18}$ (perfluorodecalin)	✓		-	-	-	2.7	57.8
	F_6H_8 (perfluorohexyloctane)	✓		-	-	-	2.5	49.1

Abbreviations: C_nH_{2n}, alkene; C_nH_{2n+2}, alkane; cSt, centistoke; ECHA, European Chemicals Agency; mN/m, millinewton/metre; PDMS, polydimethylsiloxane polymers; PFCL, perfluorocarbon liquids; SO, silicone oil.

†PFCLs can be used short term as an intra-operative tool (most common) or short-/medium-term as a post-operative tamponade. PFCLs require complete removal and exchange with another agent (fluid, air, or SO). This can be done either in the initial retinal detachment surgery (if used as an intra-operative tool) or in a secondary surgery if used a short-/medium-term post-operative tamponade. Choice of exchange agent is driven by indication.

Table 6: Ocular endotamponades and their patient-related factors

	Chemical subtype	Strict (FDP) posturing required†	1-day vision recovery‡	Need for second surgery
Conventional silicone oil[36, 42]	Conventional silicone oil (PDMS)	✓	No, vision will remain partially blurred until the oil is removed	✓
Heavy silicone oil[36, 42]	Conventional silicone oil + partially fluorinated C_nH_{2n}/C_nH_{2n+2} (PDMS + partially fluorinated alkene/alkane)	✓		✓
Gas tamponade[36, 42]	Air	✓	No, the vision is heavily blurred until the bubble is absorbed or removed	×
	SF_6 (sulphur hexafluoride)			
	C_2F_6 (perfluoroethane)			
	C_3F_8 (perfluoropropane)			
PFCL/semi-fluorinated alkanes[36, 42, 47]	C_8F_{18} (perfluoro-n-octane)	×	No, vision will remain partially blurred until PFCLs are removed	✓
	$C_{10}F_{18}$ (perfluorodecalin)	×		
	F_6H_8 (perfluorohexyloctane)	×		

Abbreviations: C_nH_{2n}, alkene; C_nH2_{n+2}, alkane; FDP, face down posturing; PFCL, perfluorocarbon liquids; PDMS, polydimethylsiloxane polymers; SO, silicone oil.
†The table summarises the most common posturing approach and does not account for patient-specific differences and/or surgeon recommendations for post-operative recovery. ‡The level of vision clarity/blur will vary with retinal problem and choice of tamponade. For gas tamponades, vision will be highly blurred until the air or gas has been reabsorbed. For SO, vision will be a little clearer than gas tamponade, but will remain partially blurred until removal.

3.1.3 Availability of technically and economically feasible alternatives

3.1.3.1 Regulatory approved OE

A list of regulatory approved OE is presented in Table 5 and Table 6.[6, 36, 41-56] There are three PFAS-free OE: air, sulphur hexafluoride (SF_6), and conventional silicone oil; however, each compound presents significant limitations in surgical practice.

3.1.3.1.1 Air

Air can be used as a short-term tamponade agent. Air is reabsorbed from the vitreous cavity within 5–7 days, compared with around 2 weeks for SF_6, 4–5 weeks for C_2F_6 and 8 weeks for C_3F_8.[36] Longer tamponade durations lead to more favourable outcomes for retinal reattachment; therefore, the short-term duration of the air tamponade may not be suitable for all RD cases and potentially increase the risk of re-detachment following surgery.[36]

Evidence has shown that air tamponade is inferior to SF_6 in achieving anatomical closure for macular holes,[57, 58] and a systematic review and meta-analysis of the efficacy of air tamponade in the treatment of RRD found that the evidence for the comparable outcomes of air to gas tamponades was low. Therefore, its use as a substitute for other tamponade agents cannot be recommended.[59]

3.1.3.1.2 SF_6

SF_6 has comparable efficacy to PFAS-containing products.[60] SF^6 is the shortest acting of the fluorinated gas tamponades, remaining in the vitreous cavity for around 2 weeks.[36] However, SF_6 is the most environmentally damaging of the OEs due to it being the most potent of the greenhouse gases, with 23,500 times the global warming potential of CO_2.[61] SF_6 has been identified in the United Nations' Kyoto Protocols and efforts are underway to reduce its use by replacing it with alternatives. A reduction in the use of SF_6 will contribute to a significant reduction in CO_2 emitted by the healthcare system, with one UK study finding that replacing SF_6 gas with other tamponade agents in RD surgery would reduce CO_2 emissions by 41–47% per hospital.[62]

3.1.3.1.3 Conventional silicone oil

There are two types of silicone oil used in retinal detachment surgery. Conventional silicone oil and heavy silicone oil, which is conventional silicone oil combined with partially fluorinated alkanes or alkenes. Silicone oil tamponades are the longest acting and remain in the eye until removed by a second surgery.[63]

The use of silicone oil tamponade is associated with complications, including development of cataracts in phakic eyes, recurrent retinal detachments, increased intraocular pressure, silicone oil emulsification and subretinal migration of the oil. In addition, the surgery required to remove the tamponade is associated with further complications and may contribute to worse outcomes.[63]

Conventional silicone oil is lighter and less dense than heavy silicone oil and is not appropriate for the treatment of proliferative vitreoretinopathy, inferior retinal tears, and macular surgery due to its buoyancy. In addition, conventional silicone oil requires post-operative posturing where patients must remain in a certain position to prevent the movement of the tamponade, which is not possible for all patients with other comorbidities or orthopaedic problems.[64]

3.1.3.2 Research and development pipeline

The targeted search of ClinicalTrials.gov identified three clinical trials that met the inclusion criteria. A summary of the three trials is presented in Table 7. The alternative agents being tested consisted of hydrogels composed of hyaluronic acid (n=2) and medium-chain triglycerides (n=1).

Table 7: Research and development pipeline

Study title	Description	Sample size	Location	Date of completion	Phase
Suprachoroidal Visco-buckling for the Treatment of Rhegmatogenous Retinal Detachment (VIKING)[65]	The study is a feasibility trial comparing standard surgery for retinal detachment (vitrectomy, cryotherapy, and gas) with a surgical variation that replaces the intraocular gas tamponade with suprachoroidal injection of viscoelastic underneath the break that caused the retinal detachment	50 patients with primary rhegmatogenous retinal detachment	UK only	December 2024 (estimated)	1
Clinical Investigation of the Safety and Effectiveness of the ABV-1701 Ocular Endotamponade[66]	The objective of the investigation is to document the safety and effectiveness of the ABV-1701 ocular endotamponade when compared with the SF_6 Gas ocular endotamponade. ABV-1701 is an injectable, *in-situ*-forming hydrogel, composed of oxidised hyaluronic acid and adipic acid dihydrazide	40 patients with uncomplicated retinal detachment	Thailand and Australia only	December 2025 (estimated)	1
Evaluating Medium-chain Triglycerides as a Temporary Intraocular Tamponading Agent for Retinal Detachment[67]	The study was a single group assessment of the use of medium-chain triglycerides as a tamponade agent during vitrectomy	10 patients with retinal detachment requiring a classical surgical procedure with silicone oil	France only	January 2023 (no results reported)	1

There are significant challenges associated with developing a suitable vitreous substitute that means even the 12-year derogation period is insufficient. Substitutes must have long-term viability and biocompatibility, ensure clear vision post-surgery, be non-toxic, provide sufficient mechanical strength, and ideally be as structurally and functionally close to the natural vitreous as possible.[67]

Hydrogels consisting of natural and synthetic polymers are being explored for their favourable properties as a vitreous substitute (high water content, high clarity, suitable density, biocompatibility) and may overcome some of the limitations of existing ocular tamponade agents, such as blurred vision following surgery and the need for a second surgery to remove silicone oil tamponades.[69] To date, studies evaluating hydrogels have focused on pre-clinical and animal models,[67] yet studies have been limited by poor transparency, deviating refractive indices, unsuitable degradation, poor biocompatibility, and toxicity.[68]

A lack of in-human evidence suggests a significant delay before alternative OE agents become widely used and available to all patients who need them.

3.2 Primary research survey

3.2.1 Sample demographics

The expert panel comprised of 16 medical professionals experienced in the conduct of vitreoretinal surgery. Primary clinical practice was in France (4, 25%), Germany (3, 18.8%), Spain (3, 18.8%), Italy (3, 18.5%) and the Netherlands (3, 18.8%), and included representatives from public (8, 50%), private (3, 18.8%) and public-private (5, 31.3%) funded settings. The panel had between 12–45 years of experience in conducting vitreoretinal surgery, with a mean of 25 years clinical experience. In total, the panel conduct approximately 8,150 vitreoretinal surgeries per year.

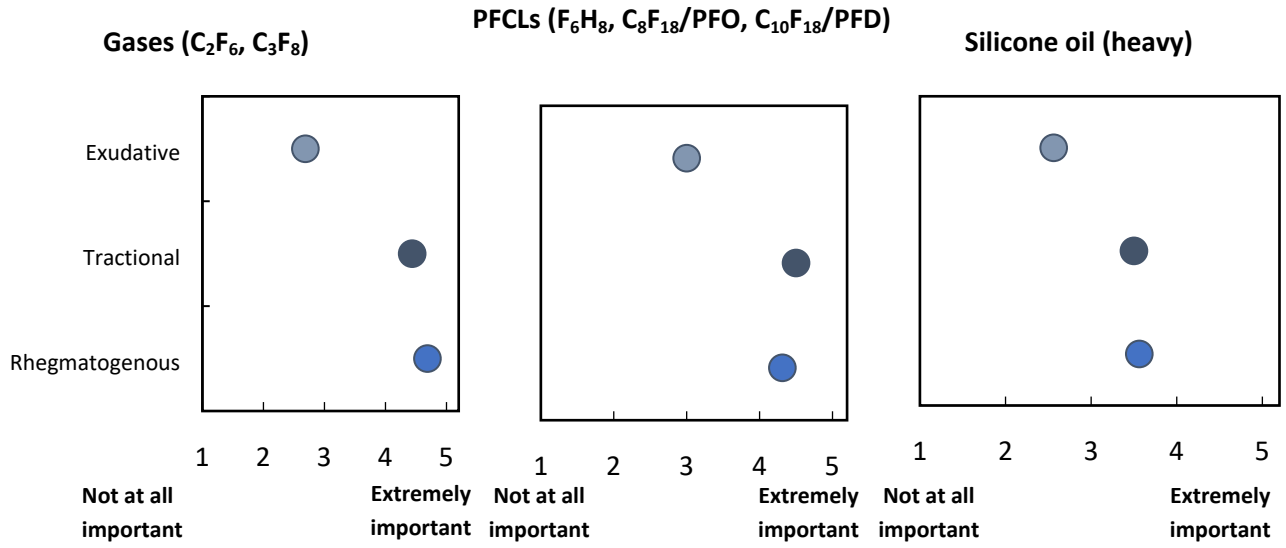
3.2.2 Surgical management of RD

The panel was invited to review Figure 1, which describes the current professional medical society recommendations for the surgical management of RD. 94% [15 of 16 respondents] validated it as an accurate depiction of current clinical practice. The panel also provided an overview of the proportion of each surgical procedure performed by pathology sub-type – the results are presented in the Appendix 2.

3.2.2.1 Role and importance of regulatory approved OE

The expert panel was invited to rate the overall importance on a scale of 1–5 (where 1 is not at all important and 5 is extremely important) of each category of PFAS-containing OE (gas, PFCL and silicone oil), for each pathology sub-type (exudative, tractional and rhegmatogenous). The results demonstrate the moderate-to-high overall importance of PFAS-containing gas ($\bar{x}$ = 2.6, 4.4, 4.6), PFCL ($\bar{x}$ = 3.0, 4.5, 4.3) and heavy silicone oil ($\bar{x}$ = 2.6, 3.5, 3.5) in exudative, tractional and RRD respectively. Surgical intervention is rarely indicated for exudative RD, explaining the lower overall importance for this sub-type. Heavy silicone oil is associated with complications such as intraocular pressure increase, emulsification, intraocular inflammation, and there is a risk of additional complications during its subsequent removal. Consequently, the panel rated heavy silicone oil as lower overall importance in the treatment paradigm.

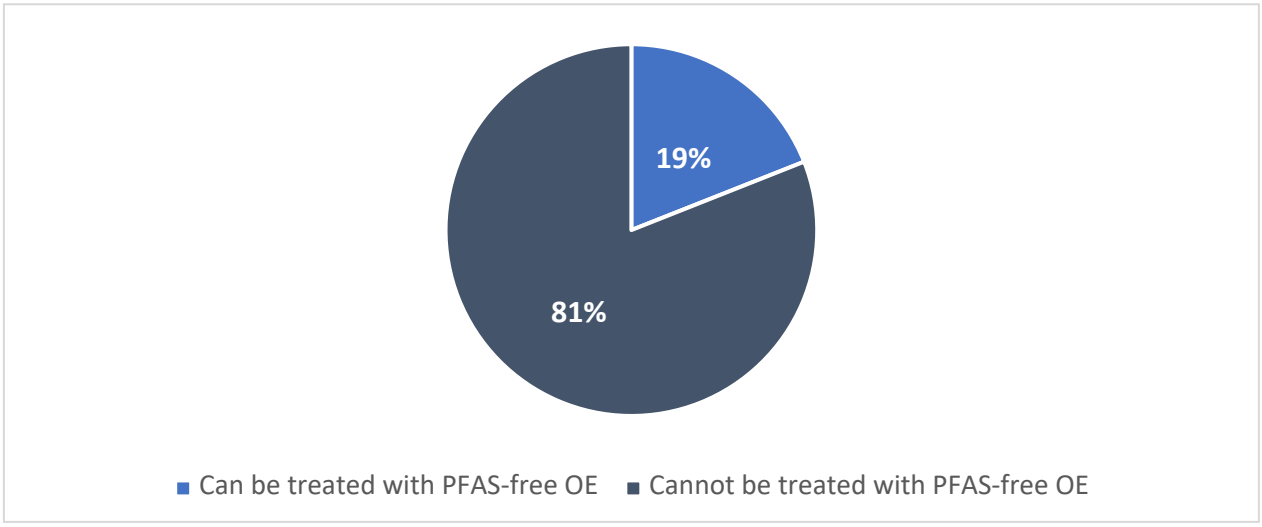
Figure 2: Importance of PFAS-containing tamponades in the surgical management of rhegmatogenous, tractional, and exudative retinal detachment



Abbreviations: PFCL, perfluorocarbon liquid; PFAS, per- and polyfluoroalkyl substances; PFD, perfluorodecalin; PFO, perfluorooctane.
Respondents were asked: Overall, how important is it to have the option of using PFAS-containing tamponades in the surgical management of retinal detachment? Please rate the importance for each type of retinal pathology and PFAS-containing product type (gases, PFCLs and heavy silicone oil). The importance was rated on a scale of 1 (not at all important) to 5 (extremely important). The average level of importance was plotted (n=16).

The panel was also invited to comment on the percentage of RD cases that could be successfully treated with PFAS-free OE including air, SF_6, and conventional silicone oil. The results demonstrate that the majority of clinical needs cannot be met with PFAS-free OE and an estimated 81% of RD cases would be left untreatable if PFAS-containing OE were removed from the market.

Figure 3: Proportion of RD cases where the clinical needs can and cannot be met with PFAS-free OE

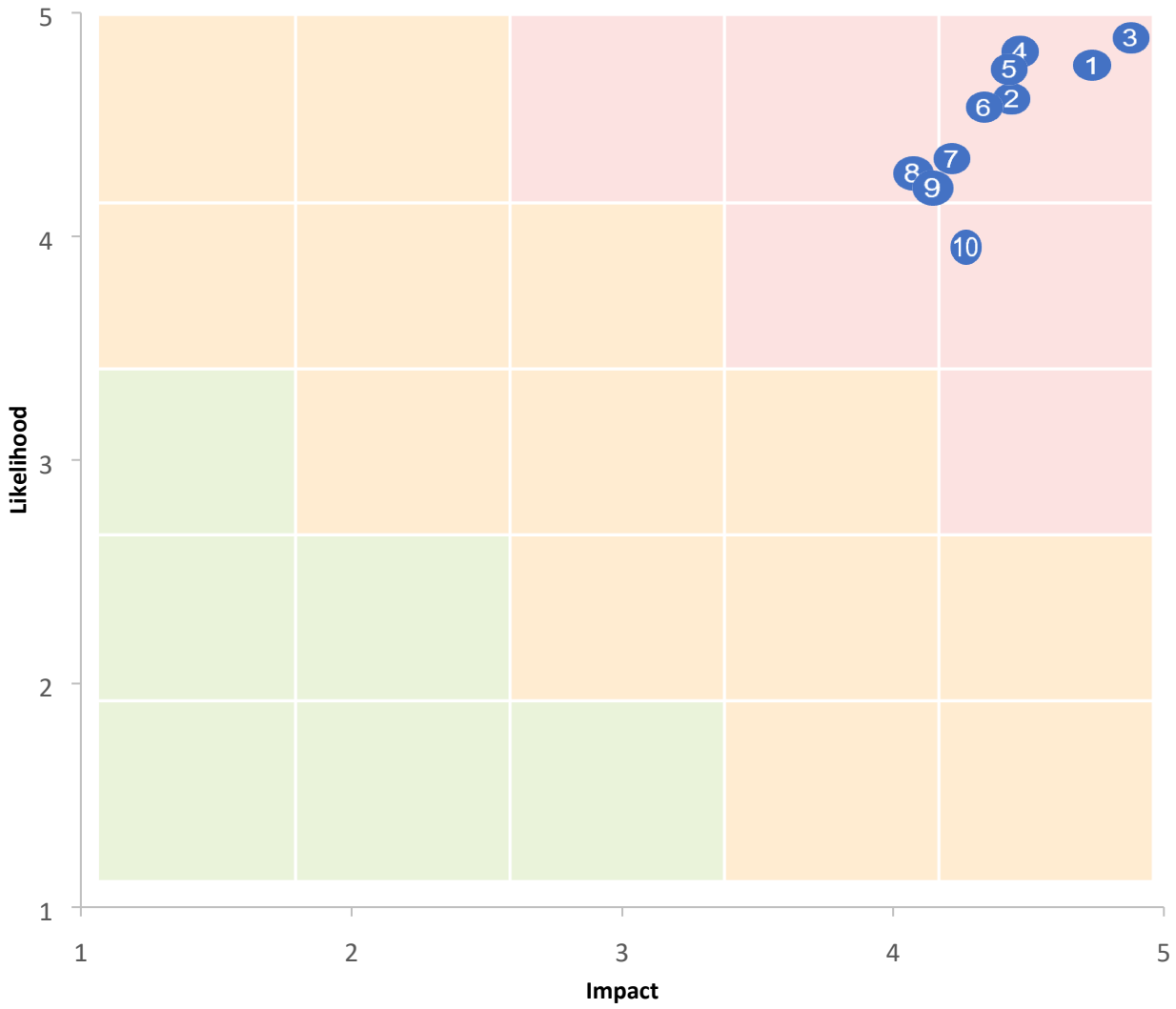


Abbreviations: OE, ocular endotamponades; PFAS, per- and polyfluoroalkyl substances; RD, retinal detachment.
Respondents were asked: Approximately, for what percentage of your current retinal detachment cases, can the clinical needs of patients be met with the current PFAS-free tamponades (air and conventional silicone oil), including all types and severities of detachments/tears? Responses were given as a percentage. Percentages from all respondents (n=16) were averaged.

3.2.3 Prospective risk and impact assessment

The expert panel was invited to participate in a prospective risk and impact assessment. Each expert independently rated the likelihood (1: not at all likely to 5: extremely likely) and impact (1: no impact to 5: severe impact) of a series of prospective patient-related outcomes, direct medical costs and indirect costs that could occur because of the proposed restriction options. All patient outcomes, direct medical costs and indirect costs were rated as high risk (red), meaning that the outcomes have a high likelihood of occurrence and a high impact (Figure 4, Figure 5, Figure 6).

Figure 4: Prospective risk-impact assessment – Patient outcomes



Key:

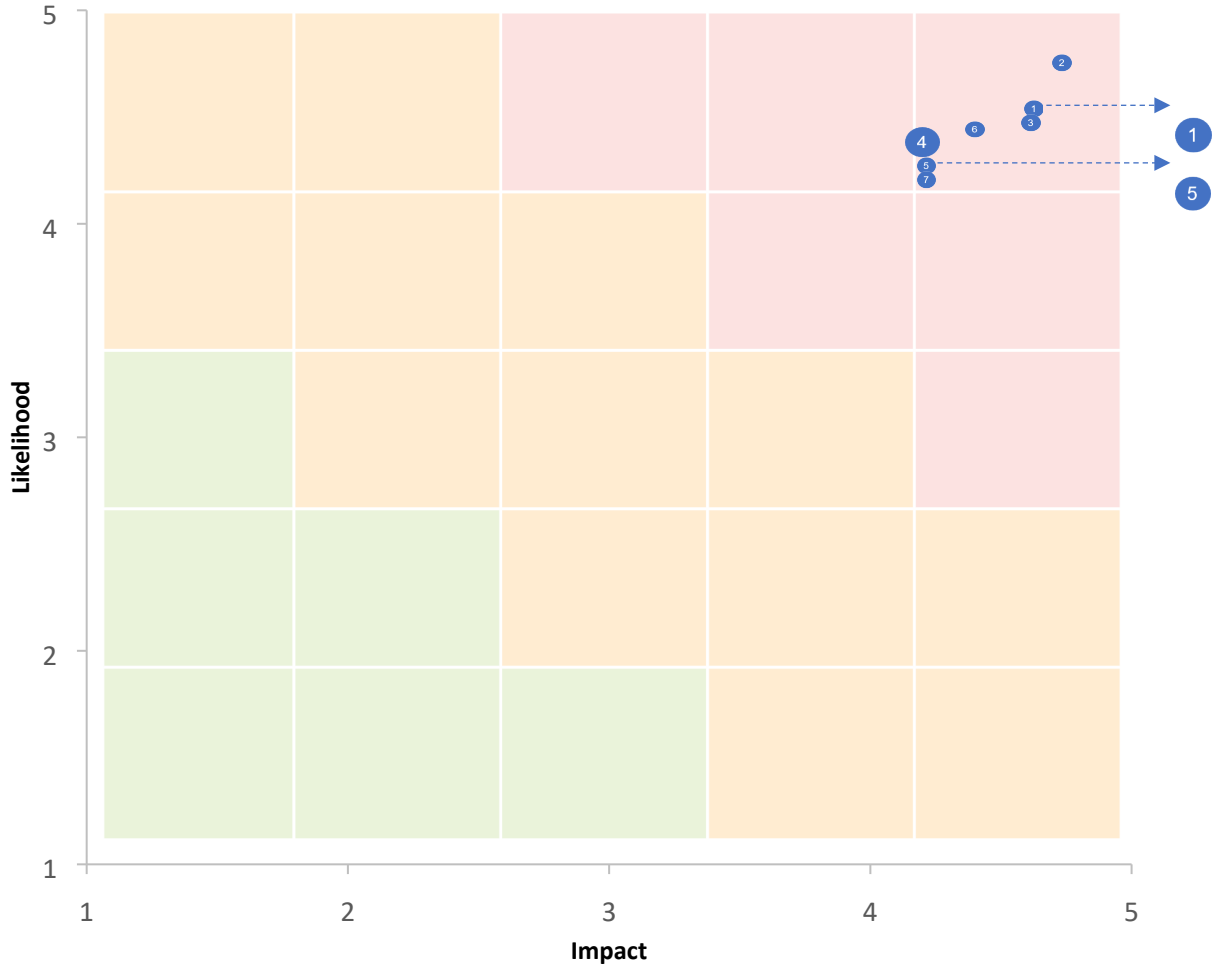
High risk	Moderate risk	Low risk

	Patient outcome	Impact: x̄	Likelihood: x̄
1.	Increased rate of anatomical failure	4.7	4.75
2.	Increased incidence of incomplete or unaddressed primary pathology	4.3	4.6
3.	Increased requirement for repeat surgeries	4.9	4.9

4. Increased number of severely visually impaired individuals	4.4	4.7
5. Increased number of legally blind patients	4.4	4.7
6. Reduction in vision related quality of life	4.3	4.6
7. Increased rates of depression, anxiety, and social isolation	4.1	4.2
8. Reduction in functional ability, including activities of daily living, mobility, and independence	4.1	4.2
9. Increased risk of falls and fall related injuries, including hip fractures	4.1	4.2
10. Increased risk of post-operative complications including cataract formation, glaucoma, keratopathy, hypotony, or haemorrhage into the vitreous cavity	4.3	4.0

Abbreviations: PFAS, per- and polyfluoroalkyl substances.
Respondents were asked: Please rate the likelihood of each of these outcomes occurring as a result of a ban on PFAS-containing substances in vitreoretinal surgery (1= not at all likely; 5= extremely likely). Please rate the impact of each of these outcomes occurring as a result of a ban on PFAS containing substances in vitreoretinal surgery (1= no impact; 5= severe impact). The average rating was plotted (n=16).

Figure 5: Prospective risk-impact assessment – Direct medical costs



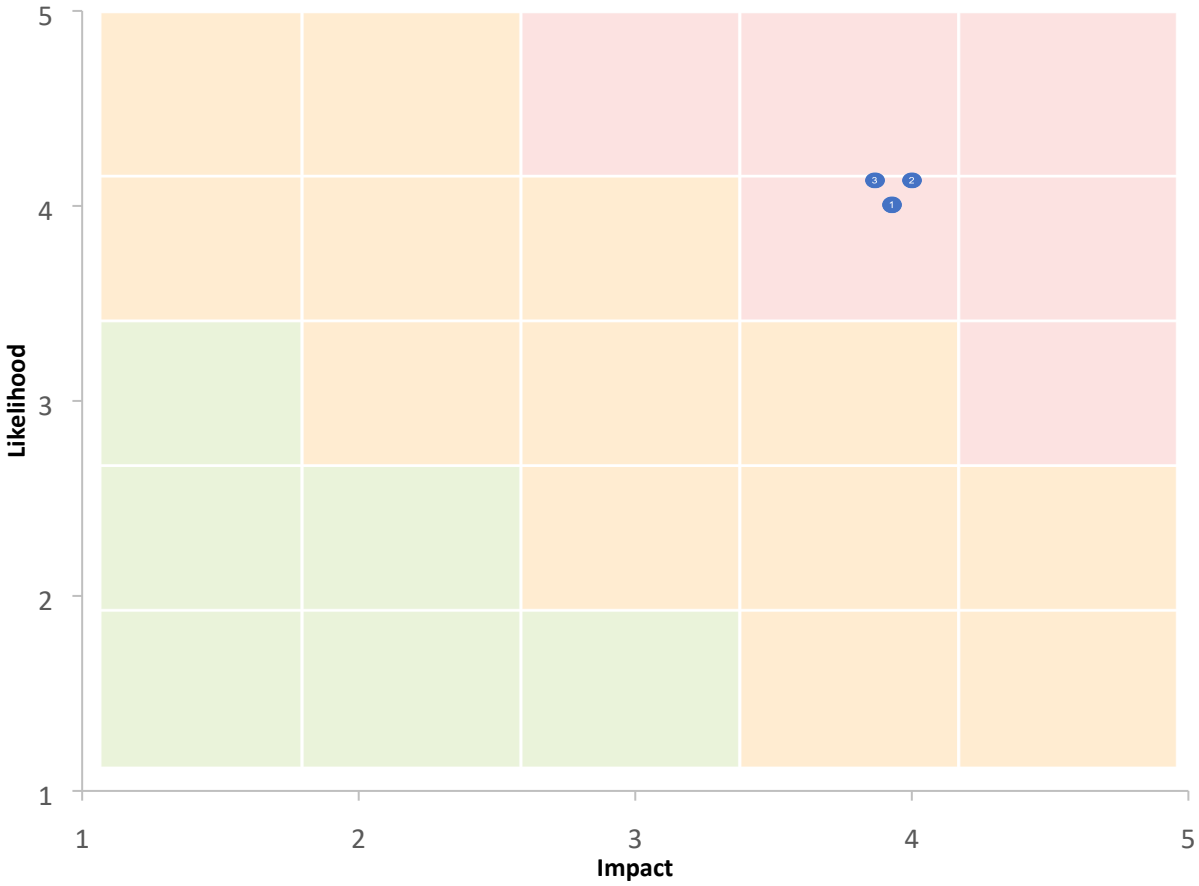
Key:

High risk	Moderate risk	Low risk

Direct medical costs	Impact: x̄	Likelihood: x̄
1) Increased healthcare resource use (HCRU), in primary and secondary care	4.6	4.5
2) Increased direct medical costs for additional surgeries	4.7	4.8
3) Increased direct medical costs for treatment of comorbidities, including anxiety and depression	4.6	4.5
4) Increased need for residential or respite care	4.2	4.4
5) Increased need for assistive technology, including home adaptations, guide cane, service dogs, alarms, vision aids etc	4.2	4.2
6) Need to train clinicians on alternative surgical techniques	4.4	4.4
7) Increased demand on social services/occupational health services	4.2	4.2

Abbreviations: HCRU, healthcare resource use; PFAS, per- and polyfluoroalkyl substances.
Respondents were asked: Please rate the likelihood of each of these outcomes occurring as a result of a ban on PFAS containing substances in vitreoretinal surgery (1= not at all likely; 5= extremely likely). Please rate the impact of each of these outcomes occurring as a result of a ban on PFAS containing substances in vitreoretinal surgery (1= no impact; 5= severe impact). The average rating was plotted (n=16).

Figure 6: Prospective risk-impact assessment – Indirect costs



Key:

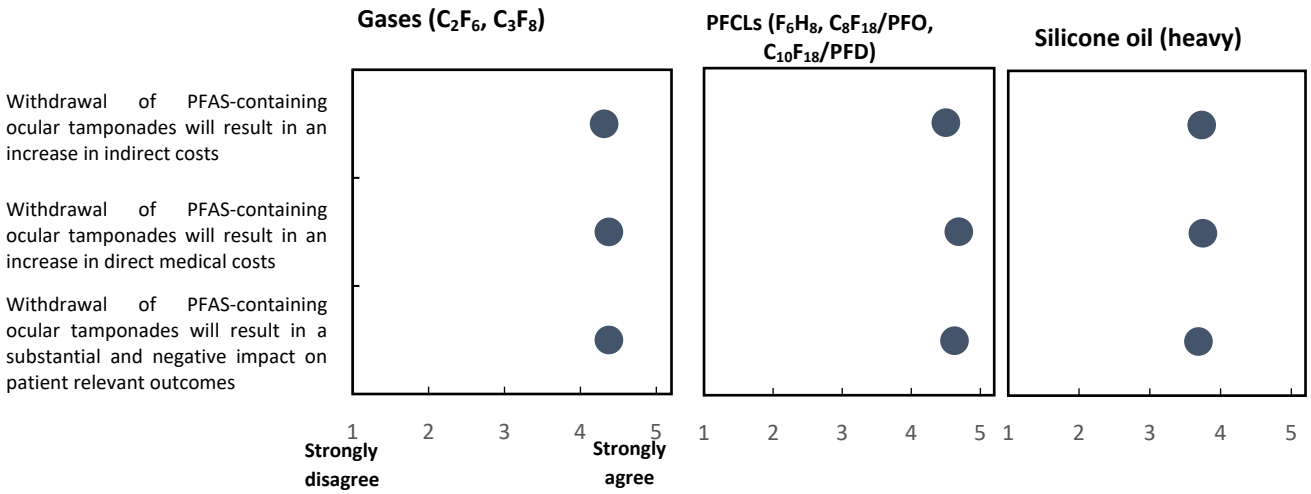
High risk	Moderate risk	Low risk

Indirect costs	Impact: x̄	Likelihood: x̄
1) Increased rates of unemployment	3.9	4.0
2) Reduction in productivity	4.0	4.1
3) Increased need for work-based assistive technology and adaptation	3.9	4.1

Abbreviations: PFAS, per- and polyfluoroalkyl substances.
Respondents were asked: Please rate the likelihood of each of these outcomes occurring as a result of a ban on PFAS containing substances in vitreoretinal surgery (1= not at all likely; 5= extremely likely). Please rate the impact of each of these outcomes occurring as a result of a ban on PFAS containing substances in vitreoretinal surgery (1= no impact; 5= severe impact). The average rating was plotted (n=16).

The expert panel was presented with statements relating to patient outcomes, direct medical costs and indirect costs, and they were invited to rate their level of agreement 1–5 (where 1 is strongly disagree, and 5 is strongly agree). The results demonstrate strong agreement that the withdrawal of PFAS-containing OE will result in a substantial and negative impact on patient-relevant outcomes [x̄ = 4.4, 4.6, 3.7] an increase in direct medical costs [x̄ = 4.4, 4.7, 3.8] and an increase in indirect costs [x̄ = 4.3,4.5, 3.7] for gases, PFCLs and heavy silicone oil, respectively. Withdrawal of heavy silicone oil was associated with a marginally lower predicted impact, since it is less frequently used due to its associated complications such as intraocular pressure increase, emulsification, intraocular inflammation, and there is a risk of additional complications during its subsequent removal.

Figure 7: Expert consensus statements: Patient outcomes, direct medical costs, and indirect costs



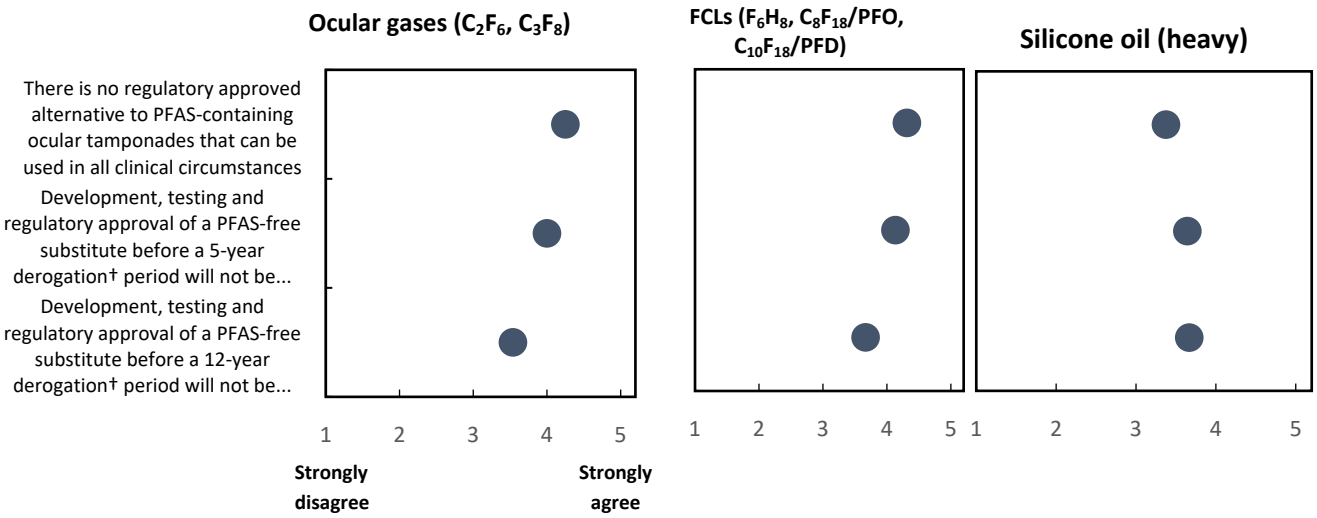
Abbreviations: PFCL, perfluorocarbon liquid; PFAS, per- and polyfluoroalkyl substances; PFD, perfluorodecalin; PFO, perfluorooctane.
Respondents were asked to rate their level of agreement with each of the statements on the Y axis for each category of PFAS-containing products. The level of agreement was rated on a scale of 1 (strongly disagree) to 5 (strongly agree). The average level of agreement was calculated from all respondents (n=16) and plotted.

3.2.4 Availability of technically and economically feasible alternatives

The expert panel was presented with statements relating to the current existence of PFAS-free alternatives, and the timeline for the development, testing and regulatory approval of a PFAS-free substitute within the 5-year and 12-year derogation periods. They were invited to rate their level of agreement on a scale of 1 to

5 (where 1 is strongly disagree and 5 is strongly agree). The results demonstrate moderate-to-strong agreement that there is no regulatory approved alternative to PFAS-containing OE that can be used in all clinical circumstances [x̄ = 4.3, 4.3, 3.4] that development, testing, and regulatory approval of a PFAS-free substitute will not be possible before a 5-year derogation period [x̄ = 4.0, 4.1, 3.6] and that development, testing and regulatory approval of a PFAS-free substitute will not be possible before a 12-year derogation period [x̄ = = 3.5 3.6, 3.6], for gases, PFCLs and heavy silicone oil, respectively.

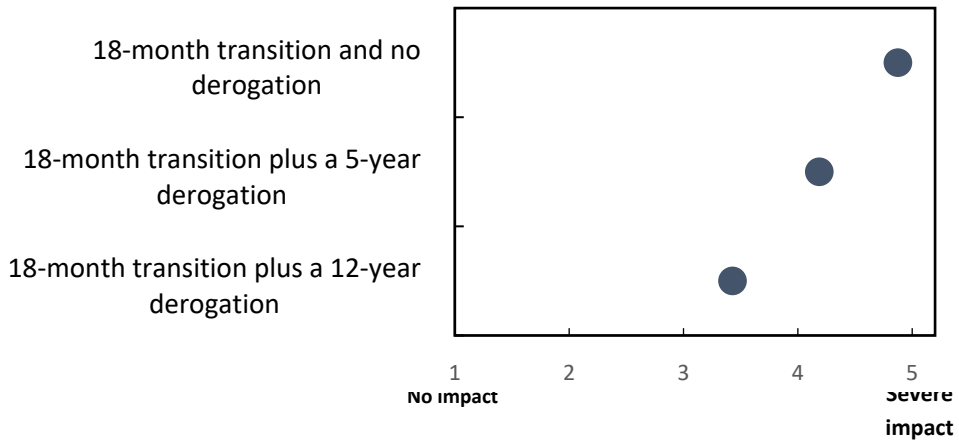
Figure 8: Expert consensus statements: timeline for the availability of technically and economically feasible alternatives



Abbreviations: PFAS, per- and polyfluoroalkyl substances; PFCL, perfluorocarbon liquids; PFD, perfluorodecalin; PFO, perfluorooctane
Respondents were asked to rate their level of agreement with each of the statements on the Y axis for each category of PFAS-containing products. The level of agreement was rated on a scale of 1 (strongly disagree) to 5 (strongly agree). The average level of agreement was calculated from all respondents (n=16) and plotted.
†A derogation is a provision that would allow for specific use-cases of PFAS to be applied differently or exempted from the EU legislation.

The expert panel was invited to rate the impact on a scale of 1–5 (where 1 is no impact and 5 is severe impact) of the timeline for RO1 (18-month transition and no derogation) and restriction option 2 (18-month transition plus either a 5-year or 12-year derogation). The results demonstrate the severe impact that RO1 (18-month transition) [x̄ = 4.9] and RO2 (18-month transition plus a 5-year derogation) would have (x̄ =4.2). The impact was less for RO2 (18-month transition plus 12-year derogation), although still moderate (x̄=3.4).

Figure 9: Impact of the timeline for the proposed transition and derogation periods

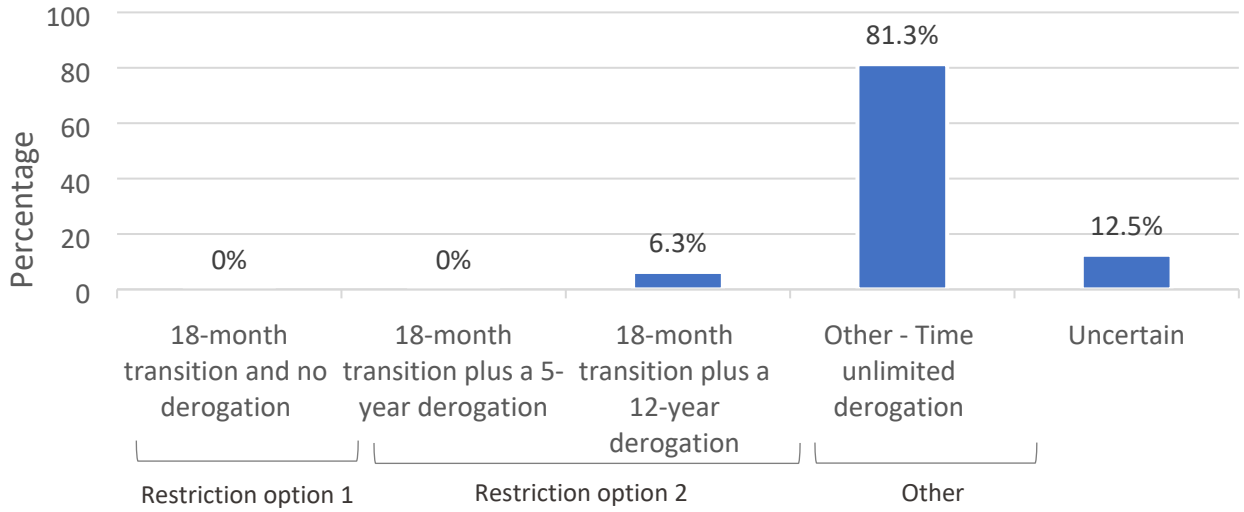


Abbreviations: PFAS, per- and polyfluoroalkyl substances.
Respondents were asked: What do you predict to be the public health impact of a total ban on the use of PFAS in ocular tamponades for vitreoretinal surgery in this patient cohort for each time scenario. The perceived impact was rated on a scale of 1 (no impact) to 5 (severe impact) for each proposed time period. The average impact was calculated from all respondents (n=16) and plotted.

3.2.5 Expert panel recommendations

The expert panel was invited to provide their recommendation on which of the proposed restriction options they would support. The results demonstrated that most of the panel supported a time-unlimited derogation (81.3%, n=13). The 6.3% (n=1) who supported an 18-month transition period plus a 12-year derogation caveated that this period should be dedicated to developing a PFAS-free alternative, and if this was not possible, the derogation period should be extended.

Figure 10: Expert panel recommendations in support of the proposed restriction options



Respondents were asked: Which restriction option would you support for this use-case? Results are plotted as a frequency distribution for N=16.

4.0 DISCUSSION

RD is a medical emergency that can be successfully managed with prompt surgical intervention.

This study has demonstrated that RD is a medical emergency that requires surgical intervention to preserve sight, functional ability, and quality of life.[4] If surgical intervention is provided promptly, RRD can achieve a primary surgical success rate of 80–90%.[13] If the RD is not treated and the detachment extends, then permanent vision loss or blindness is inevitable, with a substantial negative impact on patient outcomes, direct medical costs and indirect costs.[5]

OE have an established and critical role in the surgical management of RD.

Professional medical society guidelines (Figure 1) describe the evidence-based consensus for the surgical management of RD.[19-35] All categories of OE (gas, PFCLs and silicone oils) are used in the main surgical interventions; pars plana vitrectomy, scleral buckle and pneumatic retinopexy. The choice of OE depends upon the severity and location of the retinal detachment, patient characteristics, tamponade duration, and the specific risk-benefit profile.[6]

Gases are used in all the main surgical techniques where they are injected into the eye during surgery to flatten retinal breaks. The gas is left in the eye to be re-absorbed. C_3F_8 (PFAS-containing) and SF_6 (PFAS-free), have been the standard of care gases for 30+ years.[37]

PFCLs are used as an interoperative tool to allow for safe manoeuvres during more complex detachments, and removed at the end of surgery. Since their introduction over 40 years ago, they have become indispensable and have substantially improved surgical results.[36] C_8F_{18} and $C_{10}F_{18}$ (PFAS-containing) are routinely used to drain subretinal fluid by 43% of surgeons.[68] There are no PFAS-free PFCLs.

Silicone oils are longer-term tamponades that are reserved for severe and complex RD cases due to their significant associated complications.[39] Silicone oils must be removed by a second surgery, which is also associated with a risk of complications.[39] Conventional silicone oil is PFAS-free, while heavy silicone oil is PFAS-containing.

The panel validated the high overall importance of all categories of PAS-containing OE for the treatment of rhegmatogenous and tractional RD. Lower importance was reported for exudative RD since surgical intervention is rarely indicated.

Regulatory approved PFAS-free OE exist, but they are associated with limitations and are not suitable for all patients and clinical contexts.

Air, SF_6, and conventional silicone oil do not contain PFAS; however, they are associated with significant limitations.

Air has a short tamponade duration, which means that it is not suitable for more complex detachments, and due to its short duration in the eye, it is associated with an increased risk of detachment following surgery.[36]

SF_6 is efficacious but has a high environmental impact due to its high global warming potential.[60]

Conventional silicone oil has a high buoyancy that makes it unsuitable for some clinical contexts, and it requires post-operative posturing where patients must remain in a certain position to prevent the

movement of the tamponade, which is not possible for all patients with other comorbidities or orthopaedic problems. Furthermore, it is associated with complications, including development of cataracts in phakic eyes, recurrent RDs, increased intraocular pressure, silicone oil emulsification, and subretinal migration of the oil, and requires a second surgery to remove.

Withdrawal of PFAS-containing OE would create a significant unmet clinical need.

The panel estimate that only 19% of patients can be treated with PFAS-free OE, and if PFAS-containing OE were withdrawn from the market, then an estimated 81% of all RD cases would be untreatable. This highlights the critical importance of retaining PFAS-containing OE in the treatment paradigm.

The prospective risk impact assessment highlighted the high risk to patient outcomes, direct medical costs, and indirect costs associated with a withdrawal of PFAS-containing OE.

All patient outcomes were rated as high risk, meaning that the outcomes have a high likelihood of occurrence and a high impact. The top five patient outcomes rated as the highest risk were: increased requirement for repeat surgeries, increased rate of anatomical failure, increased incidence of incomplete or unaddressed primary pathology, increased number of severely visually impaired individuals, and increased number of legally blind patients. Similarly, direct medical costs and indirect costs were rated as high risk. This suggests that there will be a serious patient level impact, and increased economic burden to individuals, the healthcare system, and society, because of the proposed restriction.

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

The research and development pipeline contains only three Phase 1 studies that are being conducted in small cohorts, and in a small number of centres, including non-European locations (n=10–50). Consequently, they are unlikely to be representative of the entire population of patients with RD nor lead to global changes in clinical practice. The early stage of development for these substances means that there will be no new alternatives on the market at the entry-into-force date for RO1. Furthermore, in the past two decades there has been a documented increase in attrition rates and duration of clinical trials, that indicates that the 5-year and 12-year derogation periods in RO2 are also insufficient.[8] 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 1–2 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 9.5–11-years.[9] The panel also confirmed that the timelines for RO1 were insufficient, and highly challenging for RO2.

The expert panel recommended a time-unlimited derogation for this use-case.

Based upon the panel's assessment of 1) the critical and irreplaceable role of regulatory approved PFAS-containing OE; 2) the high risk to patient outcomes, direct medical costs, and indirect costs if PFAS-containing OE were withdrawn; and 3) the paucity of PFAS-free alternatives under development. A total of 81% of the experts supported a time-unlimited derogation for this use-case.

5.0 CONCLUSION

This study has demonstrated the critical role of PFAS-containing OE in the surgical management of RD. Withdrawal of the substances in the scope of this comment will result in over 80% of RD cases being surgically untreatable, with the devastating consequence of vision impairment, blindness, and other visual complications in otherwise surgically treatable eyes. Although PFAS-free options exist, they are associated with limitations in clinical practice. The expert consensus was that the proposed restriction options (RO1 and RO2) would result in a substantial and negative impact on patient relevant outcomes, direct medical costs, and indirect costs.

Furthermore, the study highlighted the non-existence of technically or economically feasible alternatives that would achieve certification or regulatory approval before entry-into-force date for RO1, and the limited number of studies in development for an alternative suggesting that there is unlikely to be an alternative that would achieve certification by the 5-year or 12-year derogation periods.

6.0 REQUEST TO ECHA

The industry stakeholder group request a time-unlimited derogation and listing in the use 'Medical devices' (Section A.3.10.1)[2] for perflunafen/perfluorodecalin ($C_{10}F_{18}$), perfluorooctane (C_8F_{18}), hexafluoroethane (C_2F_6), perfluorohexyloctane (F_6H_8), perfluoropropane (C_3F_8), and heavy silicone oil.

7.0 INDUSTRY STAKEHOLDERS SIGNATORIES

On behalf of [insert company name]: Bausch and Lomb

Signature:

Luc Bonnefoy (Sep 21, 2023, 1:22pm)

Position: President Surgical

Name (please print): Bonnefoy

Date: 21 Sep 2023

On behalf of [insert company name]: DORC

Signature:

Pierre Billardon (Sep 22, 2023, 7:05am)

Position: CEO

Name (please print): BILLARDON

Date: 22 Sep 2023

On behalf of [insert company name]: Pharmipur GmbH

Signature:

Dirk Henning Menz (Sep 21, 2023, 9:52am)

Position: CEO

Name (please print): Dr.D.-H. Menz

Date: 21 Sep 2023

On behalf of [insert company name]: Carl Zeiss Meditec AG

Signature:

Justus Felix Wehmer (Sep 21, 2023, 3:03pm)

Position: CFO

Name (please print): Justus Felix Wehmer

Date: 21 Sep 2023

On behalf of [insert company name]: Alchimia

Signature:

Bruno Chermette (Sep 21, 2023, 5:28pm)

Position: President and Ceo

Name (please print): CHERMETTE

On behalf of [insert company name]: Arcadophta

Signature:

Denis Hinaut (Sep 21, 2023, 11:24am)

Position: President

Name (please print): Hinaut denis

Date:	Date:
21 Sep 2023	21 Sep 2023

8.0 APPENDIX

Appendix 1: 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 $g \cdot mol^{-1}$

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name.

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

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name.

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·mol^{-1}

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name.

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·mol^{-1}

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name.

General	
INN	Perfluorohexyloctane
Synonyms	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorotetradecane
Molecular Formula	F_6H_8
CAS Codes	
CAS	133331-77-8
Molecular Mass	
Molecular Mass	432.26 g·mol^{-1}

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name.

General

INN	Perfluorohexyloctane and 5000 cSt silicone oil
Synonyms	1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorotetradecane + Polydimethylsiloxane
Molecular Formula	$[-Si(CH_3)2O-]n + F_6H_8$
CAS Codes	
CAS	133331-77-8†
Molecular Mass	
Molecular Mass	432.26 $g \cdot mol^{-1}$ †

Abbreviations: CAS, Chemical Abstract Service; INN, international non-proprietary name; PFAS, per- and polyfluoroalkyl substances.

† Heavy silicone oil is a mixture of silicone oil (PFAS-free) and F_6H_8 s (PFAS-containing). Therefore, the CAS code and molecular mass are provided for F_6H_8.

Appendix 2: Approximate percentage of retinal detachment surgeries that can be attributed to each surgical technique for each of the main retinal pathologies

		Type of retinal detachment					
		Rhegmatogenous		Tractional		Exudative	
		Average, %	**Range**	**Mean, %**	**Range**	**Mean, %**	**Range**
Surgical technique	Vitrectomy	44.7	0 to 95	57.7	0 to 100	32.5	0 to 100
	Vitrectomy in combination with scleral buckle	20.1	0 to 80	11.8	0 to 70	5.5	0 to 20
	Vitrectomy in combination with pneumoretinopexy	63.8	0 to 100	26.9	0 to 100	28.3	0 to 100
	Vitrectomy in combination with laser repair	64.3	0 to 100	65.5	0 to 100	40.5	0 to 100
	Scleral buckle	18.7	0 to 100	11.8	0 to 70	12.3	0 to 80
	Scleral buckle in combination with pneumoretinopexy	26.7	0 to 100	9.6	0 to 90	7.1	0 to 40
	Scleral buckle in combination with laser repair	11.5	0 to 100	16.0	0 to 100	21.1	0 to 100
	Pneumoretinopexy	2.4	0 to 10	0.5	0 to 5	2.5	0 to 20
	Pneumoretinopexy in combination with laser repair	17.3	0 to 100	0.5	0 to 5	11.7	0 to 100
	Laser repair	8.9	0 to 80	3.0	0 to 20	4.4	0 to 20
	Other	1.3	0 to 5	0.0	0 to 0	0.0	0 to 0
	Uncertain	0.0	0 to 0	0.0	0 to 0	0.0	0 to 0

Respondents were asked: In the primary treatment of retinal detachment, what proportion of all retinal detachment surgeries can be attributed to each surgical technique in your country for each of the retinal pathologies? Responses were collected as a percentage. Means were calculated from all respondents (n=16) regardless of country. Range is presented as the minimum value to maximum value.

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Thu, 21st Sep 2023 9:25:41 UTC	Sent the envelope to Justus Felix Wehmer ([redacted]@zeiss.com) for signing (95.144.71.154)
Thu, 21st Sep 2023 9:25:41 UTC	Sent the envelope to Dirk-Henning Menz ([redacted]@pharmpur.de) for signing (95.144.71.154)

Thu, 21st Sep 2023 9:25:41 UTC	Sent the envelope to Pierre Billardon ([redacted]@dorcglobal.com) for signing (95.144.71.154)
Thu, 21st Sep 2023 9:25:40 UTC	Sent the envelope to Luc Bonnefoy ([redacted]@bausch.com) for signing (95.144.71.154)
Thu, 21st Sep 2023 9:20:13 UTC	Denis Hinaut has been assigned to this envelope (95.144.71.154)
Thu, 21st Sep 2023 9:20:13 UTC	Bruno Chermette has been assigned to this envelope (95.144.71.154)
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Thu, 21st Sep 2023 9:20:13 UTC	Dirk-Henning Menz has been assigned to this envelope (95.144.71.154)
Thu, 21st Sep 2023 9:20:13 UTC	Pierre Billardon has been assigned to this envelope (95.144.71.154)
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Thu, 21st Sep 2023 9:16:55 UTC	Document generated with fingerprint 8653c8411be2e02e0fd0c8b5e6088533 (95.144.71.154)
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