Institution: University of Liverpool		
Unit of Assessment: UOA 9 - Physics		
Title of case study: Improved Treatment of Retinal Detachments Using Novel Tamponade Agents		
Period when the underpinning research was undertaken: March 2005 – July 2008		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Dr Michael Day	**Research Associate**	**2004 – Present**
Dr Michael Garvey	**Senior Research Fellow**	**1998 – 2020**
Professor Rachel Williams	**Senior Lecturer**	**1998 – Present**
Period when the claimed impact occurred: August 2013 – to date		
Is this case study continued from a case study submitted in 2014? Yes		

1. Summary of the impact

Novel silicone oil tamponades delivering improved surgical treatment of retinal detachments have been developed and commercialised, resulting in significant impacts on health and wellbeing. The products can be injected easily through fine gauge surgical needles, allowing smaller incisions, thereby minimising patient eye trauma. They also possess enhanced resistance to emulsification within the eye, reducing complications including cloudy vision, inflammation, glaucoma and retinal redetachment. Initially launched in Europe by the University of Liverpool patent licensee Fluoron GmbH, the products are now sold in approximately 40 countries and account for approximately 37% of the silicone oil tamponade market in Europe. Since end 2013, product sales globally have generated total revenue of [text removed for publication] with approximately 73,500 patients treated.

2. Underpinning research

Retinal detachment is a serious condition that without surgical treatment results in blindness. Globally, it occurs in approximately 1 in 10,000 people per annum and the only treatment is surgery. Most commonly vitreoretinal surgery is performed in which the vitreous humour is removed and replaced with a tamponade agent in order to effect retinal reattachment. In approximately 20% of cases the tamponade used is a silicone oil.

The research was conducted between March 2005 and July 2008 (with technology transfer and quality control work continuing until mid-2014) and addressed a long standing unmet need concerning the use of silicone oils (polydimethylsiloxanes – PDMS) in vitreoretinal surgery. Such oils have been used as tamponade agents since the late 1960s. Prior to the research, only two types of oil were available to surgeons, one with a viscosity of 1000mPas (millipascal-seconds) and the second with a higher viscosity of 5000mPas. The former can be injected much more rapidly into, and later removed from, the eye through fine gauge surgical needles. However it is more prone to emulsification (i.e. breakdown into small droplets) within the eye, often causing complications including cloudy vision, inflammation, glaucoma and retinal redetachment. Conversely, 5000 oil is much slower to inject and remove but less prone to emulsification. Hence, there existed an unmet need for an oil possessing both ease of injection and high resistance to emulsification. This was heightened by a trend towards using finer gauge needles in order to minimise surgical incision size and so reduce eye trauma. This trend resulted in increasing use of 1000 oil despite the higher risk of emulsification, since injection of 5000 oil through the finer needles is prohibitively slow.

The project was based in the Department of Physics in which research was designed, compositions prepared and mechanisms of emulsification within the eye studied in vitro by principal researcher and experienced surfactant chemist Dr Michael Day (Postdoctoral Research Associate). Work in the Department was supported by colloid and polymer chemist Dr Michael Garvey (then Senior Research Fellow). The project involved a

multidisciplinary collaboration with the UoL Department of Clinical Engineering, St Paul's Eye Unit (Royal Liverpool University Hospital) and the Centre For Water Soluble Polymers, Glyndwr University (Wrexham), which uniquely included all necessary expertise in surfactant and polymer chemistry, rheology, bioengineering, ophthalmology and vitreoretinal surgery. Injection speed tests and rheology measurements were performed in the Department of Clinical Engineering, UoL and the Centre for Water Soluble Polymers, Glyndwr University respectively. The team included Professor Rachel Williams (then Senior Lecturer), Department of Clinical Engineering, UoL, who provided expertise in the bioengineering of surfaces to treat retinal detachments. Expertise in vitreoretinal surgery was provided by Professor David Wong (then Consultant Vitreoretinal Surgeon, University of Hong Kong, and Honorary Professor, UoL) and Mr Theodor Stappler (then Consultant Vitreoretinal Surgeon, St Paul's Eye Unit). Rheological expertise and access to rheological apparatus was contributed by Dr Rob English (then Senior Lecturer, Glyndwr University).

Research indicated that emulsification of silicone oil within the eye results from shear forces, arising from natural eye movements, acting at the interface between the implanted oil and the surrounding residual thin aqueous (vitreous) layer remaining after surgery [3.1 - 3.3]. These forces lead to the growth (extension) of filaments of oil from the surface, which detach to form satellite droplets that become coated (i.e. emulsified) by materials present in the aqueous layer. Emulsification therefore depends on the extensional viscosity of the oil [3.2 - 3.3]. Accordingly, an increase in extensional viscosity was achieved by addition of a high molecular weight silicone polymer to a silicone base oil, alleviating filament detachment and droplet formation [3.3]. This had the additional advantage of rendering compositions shear thinning i.e. shear viscosity decreases with increasing shear force, thereby allowing rapid injection through fine gauge surgical needles [3.4].

The resulting novel tamponades Siluron 2000 and Siluron Xtra contain a silicone (PDMS) base oil in combination with silicone (PDMS) polymer to deliver this novel combination of enhanced resistance to emulsification and rapid injection speed. Densiron Xtra, a novel heavy tamponade used to treat retinal detachments in the lower part of the eye, also incorporates this technology. The technology is covered by a UoL patent filed in May 2006 that is licensed exclusively to Fluoron [3.1].

3. References to the research

3.1 Garvey MJ, Williams RL and Day M. Composition for treatment of a detached retina and method of production thereof WO 06/413269 May 2006; WO 2006/122973 November 2006; PCT EP2006/062432 (Copy available from UoL on request)

3.2 Day M, Blanchard RL, English R, Dobbie T, Williams R, Garvey M and Wong D. Shear and extensional rheometry of PDMS tamponade agents used in vitreoretinal surgery AIO Conference Proceedings Vol. 1072, pp 1411-1413, 2008; DOI: 10.1063/1.2964592

3.3 Williams RL, Day M, Garvey MJ, English R and Wong D. Increasing the extensional viscosity of silicone oil reduces the tendency for emulsification. Retina 30(2): 300-304, 2010; DOI: 10.1097/IAE.0b013e3181babe0c

3.4 Williams RL, Day M, Garvey MJ, Morphis G, Irigoyen C, Wong D and Stappler T Injectability of silicone oil based tamponade agents BJ Ophthalmol. 95: 273-276, 2011; DOI: 10.1136/bjo.2010.192344

4. Details of the impact

The University of Liverpool has developed novel silicone oil tamponades that deliver improved treatment of retinal detachments. The products can be injected easily through fine gauge surgical needles, allowing smaller incisions and thereby minimising patient eye trauma. They also possess enhanced resistance to emulsification within the eye, reducing complications including cloudy vision, inflammation, glaucoma and retinal redetachment.

The products are now sold by the University of Liverpool patent licensee Fluoron GmbH in approximately 40 countries and in Europe account for approximately 37% of the silicone oil tamponade market. Since end 2013, products sales globally have generated total revenue of [text removed for publication] with approximately 73,500 patients treated. The impacts reported are on health, wellbeing and the economy.

Product Development

The underpinning research conducted at UoL between March 2005 and July 2008 demonstrated that a silicone oil tamponade possessing a unique combination of rapid injection through fine gauge surgical needles and enhanced resistance to emulsification within the eye could be achieved by addition of a high molecular weight silicone polymer (polydimethylsiloxane – PDMS) to a base silicone (PDMS) oil, thereby addressing a long standing unmet need for such a product in vitreoretinal surgery [3.1 - 3.4]. Additionally, such compositions are chemically identical to conventional oils, greatly simplifying regulatory approval.

The technology is covered by a UoL patent filed in 2006 (WO2006/122973 – *"Composition for the treatment of a detached retina and method of production thereof"*; Inventors Rachel Williams, Michael Garvey, Michael Day) [3.1]. In December 2005 the technology was licensed exclusively to Fluoron GmbH (Magirus-Deutz-Strasse 10, D-89077 Ulm, Germany; contact Dr Wilfried Kugler), a leading global supplier of silicone oil tamponades, with the company agreeing to pay all future patent costs.

Following technology transfer from the UoL, Siluron 2000 (EC Certification: CE 575554) was launched by Fluoron in Europe in 2008 [5.1; 5.2]. The product has a much lower shear viscosity (approximately 2300mPas) than conventional 5000 silicone oil and (unlike the latter) is shear thinning and so can be injected approximately 3 times as rapidly as 5000 oil whilst possessing similar emulsification resistance [3.2 - 3.4].

This was followed in July 2013 by Siluron Xtra (EC Certification: CE 575554) [5.1; 5.2]. Compared to Siluron 2000, Xtra contains a higher amount of silicone polymer, increasing the extensional viscosity and therefore further enhancing resistance to emulsification [3.2 - 3.4]. The product has a shear viscosity of approximately 4600mPas and (again due to shear thinning) can be injected approximately twice as rapidly as conventional 5000 silicone oil [3.4].

A third product, Densiron Xtra, a "heavy tamponade" tailored specifically for the treatment of retinal detachments in the lower part of the eye, was launched in 2016 [5.2]. This delivers enhanced resistance to emulsification compared to other heavy tamponades (with this product more rapid injection is not advantageous since existing heavy tamponades are already easy to inject).

Economic Impact

The UoL technology is unique and distinguishes Fluoron's products from those of competitor suppliers of standard silicone oil tamponades. By end 2013, the UoL patent had been granted in Australia, China, Hong Kong and Japan. Since end 2013, the patent has been granted in Canada (2015), the EU (2015) and Turkey (2015) and is currently pending in the USA.

Globally, the annual incidence of retinal detachments is approximately 1 in 10,000 people. In Europe there are approximately 80,000 cases per annum with approximately 20,000 being treated with a silicone oil tamponade. In 2019, combined European sales of Siluron 2000, Siluron Xtra and Densiron Xtra were approximately 7,540, indicating a market share of approximately 37% (5.3]. Globally, between end 2013 and end June 2020, combined sales of the products were 77,224 generating total revenue of [text removed for publication] (compared to total unit sales and revenue between 2008 and end 2013 of 38,736 and [text removed for publication] respectively) [5.3].

Impacts on Health and Wellbeing

The novel products have transformed the treatment of complex retinal detachments by combining the advantages of conventional silicone oil tamponades whilst alleviating the drawbacks, thereby improving patient outcomes. Between end 2013 and end June 2020, approximately 73,500 patients have been treated and therefore benefited from the technology. Testimonials from internationally leading vitreoretinal surgeons evidence benefits to health:

- "*The introduction of the oils has in my mind already saved a lot of eyes from complications and costs of treating these complications… I fully endorse the invention and I regard it as one of the UK's best contributions to the field of vitreoretinal surgery*" - Consultant Vitreoretinal Surgeon (Retired), St Paul's Eye Unit, Royal Liverpool University Hospital [5.4]

- "*From a patient perspective emulsification resistance remains the paramount quality of any silicone oil since it is thought that it was precisely the emulsified droplets that give rise to postoperative ocular inflammation, glaucoma and ultimately sight loss. Herein lies the patient benefit in choosing a medical device (silicone oil) with a reduced tendency to emulsify. In essence, it is a better product*" - Consultant Vitreoretinal Surgeon, Hospital Ophthalmic Jules-Gonin, Lausanne [5.5]

Prior to this research, surgeons were faced with a choice between ease of injection with a greater risk of emulsification or greater emulsification resistance but with much slower injection, with the trend towards finer gauge surgery often leading surgeons to opt for 1000 oil with the associated greater risk of emulsification-related complications such as impaired vision, inflammation, glaucoma and retinal redetachment. With Siluron 2000 and Siluron Xtra, rapid injection offers shorter operating times and compatibility with finer gauge surgical needles, the latter allowing for smaller surgical incisions, thereby minimising patient eye trauma; enhanced emulsification resistance reduces the risk of patients suffering post-operative complications, thereby reducing the likelihood of further treatment being required and hence reducing costs to (for example) the NHS and improving patient wellbeing. Testimonials from Clinicians within the NHS have described the impact on their practice:

- "*Before the launch of Siluron 2000 and Siluron Xtra I was using 1000 centistoke oil but have now switched to Siluron 2000 where I want a light (i.e. buoyant) oil and Densiron Xtra for situations where I want to use a heavy oil… I have found a low incidence of emulsification, significantly improved compared to the previous oils…The ability to inject and extract the oils even with 25 gauge surgery is also much improved compared to high viscosity oils… Siluron 2000 and Siluron Xtra have been major advances for vitreoretinal surgery*" - Consultant Ophthalmologist, Sunderland Eye Infirmary [5.6]

- "*Vitreoretinal surgeons aim to remove the silicone oil after 3 months because of the risk of emulsification leading to complications with keratopathy, disease of the cornea and glaucoma… in my experience such complications have been much less with Siluron 2000 and Siluron Xtra*" - Consultant Vitreoretinal Surgeon, St Paul's Eye Unit, Royal Liverpool University Hospital [5.7]

The efficacy of the products has been confirmed in reported studies. Stalmans et al (72 patient study, 2015) reported that Siluron 2000 could be injected and removed significantly more rapidly than standard 5000 oil and showed similar emulsification behaviour [5.8]. Hussain et al (28 patients, 2017) concluded that Siluron Xtra "seems to be an acceptable alternative tamponade for the management of complex retinal detachments with comparable anatomical success… to other low viscosity silicone oil agents but more importantly with a lower rate of emulsified oil-related complications" [5.9]. An in-vitro study by Chan et al (2017)

reported that Siluron 2000 emulsified less than a viscosity-matched standard 2000 oil and Siluron Xtra emulsified less than standard 5000 oil [5.10].

In summary, the novel silicone oil tamponades have had a significant impact on patient outcomes with health benefits including reduced eye trauma and reduced post-operative complications. In Europe, the products have achieved approximately 37% share of the silicone oil tamponade market. The products have had global reach through sales in approximately 40 countries, generating total revenue of [text removed for publication] and being used to treat approximately 73,500 patients.

5. Sources to corroborate the impact

5.1 Fluoron product brochure describing Siluron 2000 and Siluron Xtra
5.2 Fluoron product brochure including description of Siluron 2000 and Siluron Xtra, pages 18-21, and description of Densiron Xtra, pages 22-25
5.3 Unit sales and revenue data received from Fluoron (source statements available from the UoL on request)
5.4 Testimonial from Consultant Vitreoretinal Surgeon (Retired), St Paul's Eye Unit, Royal Liverpool University Hospital; Honorary Professor to the Department of Eye and Vision Science, University of Liverpool; Former Chair and Head of Department of Ophthalmology, University of Hong Kong, endorsing safety and efficacy of Siluron 2000 and Siluron Xtra (contact details provided)
5.5 Testimonial from Consultant Vitreoretinal Surgeon, Hospital Ophthalmic Jules-Gonin, endorsing enhanced emulsification resistance of Siluron 2000 and Siluron Xtra
5.6 Testimonial from Consultant Vitreoretinal Surgeon, Sunderland Eye Infirmary, endorsing Siluron 2000 and Siluron Xtra as major advances in vitreoretinal surgery
5.7 Testimonial from Consultant Vitreoretinal Surgeon, St Paul's Eye Unit, Royal Liverpool University Hospital, endorsing reduced complications when using Siluron 2000 and Siluron Xtra
5.8 Stalmans P, Pinxten AM, Wong DS. Cohort safety and efficacy study of Siluron 2000 emulsification resistant silicone oil and F4H5 in the treatment of full thickness macular hole. Retina 2015 Dec; 35(12): 2558-2566 DOI: 10.1097/IAE 0000000000000647
5.9 Hussain RN, Myeni J, Stappler T and Wong D. Polydimethylsiloxane as an internal tamponade for vitreoretinal surgery. Ophthalmologica. 2017; 238(1-2): 68-73. DOI: 10.1159/000470850. Epub 2017 Apr. 19.
5.10 Chan YK, Czanner G, Shum HC, Williams RL, Cheung N and Wong D. Towards better characterization and quantification of emulsification of silicone oil in vitro. Acta Ophthalmoligica 2017, Aug; 95(5); pp. 385-392 DOI: 10.1111/aos.13258 Epub 2016 Oct. 24.