

Institution: The University of Liverpool		
Unit of Assessment: UoA12 Engineering		
Title of case study: Development of Novel Tamponade Agents has Improved the Treatment of Retinal Detachment		
Period when the underpinning research was undertaken: 2006 – 2014		
Details of staff conducting the underpinning research from the submitting unit:		
Names(s):	Roles(s) (e.g. job title):	Period(s) employed by submitting HEI:
RL Williams	Professor	1998 – present
RJ Poole	Professor	2002 – present
VR Kearns	Senior Lecturer	2008 – present
MJ Day	Research Associate	2004 – present
MJ Garvey	Senior Research Fellow	1998 – present
Period when the claimed impact occurred: 1 st August 2013 – 31 st July 2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact</p> <p>Silicone oil tamponades for improved surgical treatment of retinal detachments have been developed; Siluron 2000, Siluron Xtra and Densiron Xtra. These are engineered to enable rapid injection through finer gauge needles, allowing smaller incisions and thereby minimising eye trauma. They also possess high emulsification resistance within the eye, hence reducing complications including cloudy vision, inflammation, glaucoma or retinal re-detachment. The products were launched in Europe by the UoL patent technology-licensee Fluoron GmbH and are currently sold in approximately 40 countries. From 2014 to 2020 they have been used to treat in excess of 77,000 patients.</p>		
<p>2. Underpinning research</p> <p>2.1 Background and context: Retinal detachment is a serious condition affecting all age groups that if left untreated results in blindness. For complex retinal detachments vitreoretinal surgery is performed, whereby the vitreous body of the eye is removed and an implant known as a retinal tamponade is inserted, in order to hold the retina in place until reattachment occurs (typically 3-6 months). The annual incidence of retinal detachment globally is approximately 1 in 10,000 people with approximately 80,000 cases per annum in Europe alone; in approximately 20,000 of these cases the tamponade agent used is a silicone oil. The incidence of retinal detachment is rising due to the increase in diabetes causing ocular complications. A common concern of silicone oil tamponades is emulsification which can cause significant clinical complications such as cloudy vision, inflammation and glaucoma. It is reported that emulsification is seen in all eyes that have had silicone oil present for at least 1 year so most surgeons recommend removing this type of tamponade within 12 months of surgery.</p> <p>To increase the emulsification resistance most producers increased the viscosity but this made the oil more difficult to inject into (and later remove from) the eye. In addition, various semi-fluorinated alkanes were added to the oil to increase the specific gravity (heavy tamponades) to improve treatment of retinal detachments in the lower half of the eye but this significantly reduced the viscosity increasing the risk of emulsification. Hence, there has been an unmet need for oils that display ease of injection, high resistance to emulsification and may have a specific</p>		

gravity greater than 1. This has been heightened by a trend towards the use of finer gauge needles in order to minimise surgical incision size and so reduce eye trauma.

2.2 Underpinning research: The emulsification of silicone oils in the eye is due to a combination of high shear forces, insufficient interfacial tension between the oil and aqueous phases in the eye, and the presence of proteins that both lower the interfacial tension and stabilise emulsified droplets. A multidisciplinary team from the University of Liverpool, led by Professor Rachel Williams and including input from colloid scientists, Dr Michael Garvey and Dr Michael Day, Professor Robert Poole, expert in complex fluids and rheology and vitreoretinal surgeons Mr David Wong and Mr Theodor Stappler, developed a strategy to modify the material properties of the oils by increasing their extensional viscosity. This was achieved by considering the composition of the oil and adding a high molecular weight silicone polymer to a low viscosity silicone oil to change its rheological properties. In addition to increasing extensional viscosity, the high molecular weight additive promotes shear thinning of the fluid during injection. We engineered novel compositions and this was filed for a patent [3.1]. This resulted in the production of a silicone oil (Siluron 2000) with a clinically appropriate shear viscosity and a higher emulsification resistance than existing oils [3.2-3.4]. Further development, in collaboration with Fluoron GmbH, produced a product with a further addition of the high molecular weight component resulting in an oil with an even higher emulsification resistance (Siluron Xtra) that is still injectable. These oil combinations allowed rapid injection through fine gauge surgical needles [3.5]. The same principle was applied to the production of a 'heavy' tamponade [3.6] using a combination of silicone oil, semi-fluorinated alkanes and high molecular weight silicone polymer called Densiron Xtra.

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 2006/122973 (granted EP-1881818 B1: Austria, Belgium, France, Germany, Hungary, Ireland, Italy, The Netherlands, Poland, Portugal, Slovenia, Sweden, Switzerland, Turkey; Australia-2006248902; China-ZL200680017414.9; Canada-2608571; Hong Kong-HK 1119394; Japan-5198259; US 10363315 B2)
- 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. AIP Conference Proceedings, 1027:1411-1413, 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 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 Ophthalmologica*, 95(5): E385-E392, 2017; DOI:10.1111/aos.13258
- 3.5 Williams RL, Day MJ, Garvey MJ, Morphis G, Irigoyen C, Wong D and Stappler T Injectability of silicone oil-based tamponade agents *British Journal of Ophthalmology* 95: 273-276, 2011; DOI: 10.1136/bjo.2010.192344
- 3.6 Caramoy A, Kearns VR, Chan YK, Hagedorn N, Poole RJ, Wong D, Fauser S, Kugler W, Kirchhof B, Williams, RL. Development of emulsification resistant heavier-than-water tamponades using high molecular weight silicone oil polymers. *Journal of Biomaterials Applications*, 30(2): 212-220, 2015; DOI:10.1177/0885328215575623

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Further work funded by Fluoron GmbH, “Producing novel tamponade agents”, 2007 – 2008, GBP58,629; PI Professor Rachel Williams.

4. Details of the impact

4.1 Superior tamponade agents reduce surgical trauma and reduce complications:

Following treatment for retinal detachment complications can occur including cloudy vision, inflammation, glaucoma and retinal redetachment. We have developed silicone oil tamponades, that, unlike conventional oils, can be both rapidly injected through fine gauge surgical needles, allowing smaller surgical incisions and hence reduced eye trauma, and possess good resistance to emulsification within the eye, alleviating these complications. We have demonstrated that the rate of injection is 50% more rapid than the standard oils through a 20 gauge needle and furthermore that the new oils can be injected through a smaller 23 gauge needle which is not possible with the standard oil [3.5]. Additionally, the high molecular weight component is chemically identical to the poly(dimethyl siloxane) base oil (differing only in molecular weight), which reduced the time to obtain regulatory approval.

4.2 Delivering the Impact: A UoL patent was filed in 2006: WO2006/122973 – “Composition for the treatment of a detached retina and method of production thereof” and licensed to Fluoron GmbH (Magirus-Deutz-Strasse 10, D-89077 Ulm, Germany) in December 2005 with Fluoron agreeing to pay all future patent costs. The patent is now granted around the world [3.1]. Fluoron GmbH develops and manufactures ultrapure innovative biomaterials for retinal and cataract surgery. In this field, Fluoron GmbH plays a worldwide leading role in providing ophthalmic surgeons with creative and efficient solutions and consolidates its international competitive position by acquiring extensive intellectual property rights. The company's competence focuses on the development, manufacture and marketing of light and heavy tamponades for retinal surgery, perfluorohydrocarbons and semifluorinated alkanes as temporary tamponades, as well as dyes for anterior and posterior segment surgery [5.1]. Siluron 2000, based on our patented technology, was launched in Europe by Fluoron and has a lower shear viscosity than the standard oil and (unlike the latter) is shear thinning and so can be injected faster whilst possessing similar emulsification resistance. A second product also based on our technology, Siluron Xtra, contains more polymer (10%) for further enhanced emulsification resistance. This has a shear viscosity similar to the standard oil but (due to shear thinning) can be injected faster. These products have been sold worldwide since 2014.

Densiron Xtra was launched in January 2016 which uses our patented technology to increase its emulsification resistance. It is a ‘heavier-than-water’ tamponade which has an important clinical application in the treatment of retinal detachments in the lower half of the eye. This overcomes the need for the patient to lie face down for several days, called posturing, which is particularly uncomfortable for older patients. This product has virtually replaced Fluoron’s standard heavy tamponade [5.2] in their sales figures.

Operations Manager, Fluoron GmbH notes “... *the high molecular weight family of silicone oils, i.e. Siluron® 2000, Siluron® Xtra and Densiron® Xtra, added a set of meaningful and valued differences to distinguish Fluoron’s offering from competitors’ offerings. In 2018 the share of Siluron® 2000 and Siluron® Xtra was 38.2% of all silicone oil units sold compared to 44.4% of Siluron® 5000. This enabled Fluoron GmbH to successfully consolidate an internationally competitive position in the provision of innovative and efficient solutions for retinal surgeons.*” [5.3 a]. A TMR report states that “*Global vitreous tamponades market is expected to reach USD77,500,000 globally in 2020*”. It reports that the silicone oil component of the market is expected to grow the fastest during the period 2014-2020. Fluoron GmbH market these new

silicone oil products as “A new generation of silicone oils with an innovative molecular design”. Although they still sell their standard silicone oils they describe Siluron 2000 and Siluron Xtra as “premium silicone oils”. From 2014 to 2020 they have been used to treat in excess of 77,000 patients [5.3 b].

4.3 Performance evaluation: Three in vitro emulsification studies have been reported. Two report that Siluron 2000 emulsified less than standard oils [5.4; 5.5], one also reports that Siluron Xtra emulsified less than these oils and also less than Siluron 2000 [5.5]. In a third study, Siluron 2000 and Siluron Xtra emulsified less than a viscosity-matched standard oil [3.4].

The ultimate beneficiaries are patients with access to improved tamponades that combine rapid injection through finer gauge needles (minimising trauma) with good emulsification resistance (fewer clinical complications). Since 2015 initial clinical studies on the outcomes of Siluron 2000 and Siluron Xtra have been reported in the literature. These studies are designed to evaluate ‘safety and equivalence’ only and so can only conclude this level of outcome.

An assessment of Siluron 2000 involving 20 patients was carried out at St Paul’s Eye Unit, Royal Liverpool University Hospital. Clinically, it was reported that “*anatomical success rates were comparable to our experience with standard 5000 mPas oil, so was its safety profile*” [5.6]. Stalmans et al (2015; 72 patients) [5.7] reported that Siluron 2000 could be injected and removed significantly more rapidly than standard oil and showed similar emulsification behaviour. Hussain et al (2017; 28 patients) [5.8] reported 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*”. Stebnev et al (2017; 56 patients) [5.9] reported the “safety and efficacy” of Siluron 2000 in patients with tractional diabetic retinal detachment. A recent review [5.10] of treatment of retinopathy of prematurity, a serious sight-threatening complication of premature babies says “*The recent introduction of semifluorinated heavy silicone oil (Densiron Xtra) is promising in improving results of surgery.*”

Recent quotations from surgeons on their opinion of Densiron Xtra [5.1] include: Densiron Xtra is “*Easy to inject and aspirate, decreased emulsification rate, yet heavy tamponade agent.*” “*I use Densiron Xtra because I feel more secure in complicated retinal detachments with pathologies in the inferior segment for elderly patients for whom correct patient positioning cannot be guaranteed.*” and “*The quality that I appreciate most is the ease of injection, even with 25G. Also, its intraocular tolerance and stability against emulsification is appreciable..... these qualities make Densiron Xtra an important ally in complex vitreo-retinal surgery improving its prognosis.*”

5. Sources to corroborate the impact

5.1 Innovative Biomaterials for Retinal Surgery. Fluoron GmbH product brochure (includes details of properties and applications of Siluron 2000 and Xtra, p18, Densiron Xtra, p22, and clinician testimonials p24) accessed 30 11 20
https://www.geuder.de/fileadmin/images/Produkte/Biomaterialien/69407_Fluoron_Gesamtbrochure_EN_2019-05_web.pdf

5.2 Press release by Fluoron GmbH on the launch of Densiron Xtra January 2016 (.pdf)
 Web-site accessed 30 11 20

https://www.geuder.de/en/news-events/press-center/press-releases/?tx_news_pi1%5Baction%5D=detail&tx_news_pi1%5Bcontroller%5D=News&tx_news_pi1%5Bnews%5D=22&cHash=a9088ae09904af5147311a5bace08aed

- 5.3 a) Statement, May 2019, from Operations Manager Fluoron GmbH (.pdf) – demonstrating the contribution of our technology in providing Fluoron with a competitive advantage over other silicone oil suppliers and provide innovative and efficient solutions for surgeons
- b) Letter, 26 11 20, from University of Liverpool (.pdf) giving annual sales data for licenced Fluoron Silicone Oil Tamponade products
- 5.4 Caramoy A, Schroder S, Fauser S and Kirchof B. In vitro emulsification assessment of new silicone oils. Br J Ophthalmol. 2010; 94: 509-512 DOI:10.1136/bjo.2009.170852 demonstrating increased emulsification resistance of our patented technology
- 5.5 Caramoy A, Hagedorn N, Fauser S, Kugler W, Grob T and Kirchof B. Development of emulsification-resistant silicone oils: Can we go beyond 2000 mPas silicone oil? Investigative Ophthalmology and Visual Science 2011; 52 (8): 5432-5436 DOI:10.1167/iops.11-7250 demonstrating further improvement of emulsification resistance of Siluron Xtra compared to Siluron 2000
- 5.6 Stappler T, Konstantinidis L and Wong D. Siluron 2000 novel generation silicone oil: Proof of concept and one year clinical results. ARVO Annual Meeting Abstract March 2012 Invest. Ophthalmol. Vis. Sci. 2012; 53: E-Abstract 5792. – .pdf demonstrates clinical safety and efficacy
- 5.7 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 – demonstrating favourable clinical use and handling in comparison with standard oils in a large patient cohort
- 5.8 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. – reporting clinical efficacy and safety
- 5.9 Stebnev S, Stebnev V, Malov I. Microinvasive vitrectomy 25 gauge in the treatment of patients with tractional diabetic retinal detachment. Bulletin of Science and Practice 2017, 12:198-203 DOI:10.5281/zenodo.1112393 – English language abstract with Russian Language paper,- demonstrating efficacy and safety in an international cohort of patients with diabetic retinopathy
- 5.10 Othman IS. Retinopathy of prematurity: A major review and situation analysis in Egypt. J Med Sci Res 2018; 1 (3):136-144 DOI: 10.4103/JMISR.JMISR_37_18 demonstrating significant opportunity to improve treatment to save sight in babies with retinopathy of prematurity