Institution: Queen Mary University of London		
Unit of Assessment: 3		
Title of case study: Developing Unique Bioactive Glasses to Create the World's First 'Smart' Toothpaste		
Period when the underpinning research was undertaken: 2009 - present		
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:**
1) Robert Hill	1) Professor of Physical Sciences in relation to Dentistry	1) 10/2008 - present
2) David Gillam	2) Reader, Institute of Dentistry	2) 2009 - present
3) Natalia Karpukhina	3) Reader, Institute of Dentistry	3) 2010 - present
4) Delia Brauer	4) Research Fellow, Institute of Dentistry	4) 2009 - 2013
Period when the claimed impact occurred: 08/2013 - present		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Patented bioactive glasses developed by dental materials experts at Queen Mary led to the spin out of BioMin Technologies Ltd in 2014. Their toothpaste BioMinF® is based on these glass particles, which form fluorapatite that protects teeth from decay and reduces sensitivity and pain. Launched in 2016, BioMinF is the first toothpaste in the world to incorporate the slow release of fluoride over 10-12 hours, with six clinical trials showing that BioMinF is twice as more effective at relieving pain than other leading sensitivity toothpastes. BioMinF containing toothpastes are now sold in over 30 countries worldwide either under licensing or distribution agreements. This generates over GBP500,000 in annual revenue for BioMin Technologies Ltd, with over 100,000 tubes being produced every month. In 2019, BioMinF was named the UK's best oral sensitivity relief provider in the Healthcare & Pharmaceutical Awards. It is the first toothpaste to be accredited for dentine hypersensitivity and tooth remineralisation by the Oral Health Foundation.

2. Underpinning research

Fluoride in toothpaste plays a vital role in preventing tooth decay and promoting remineralisation of teeth, helping them to resist decay. However, most of the fluoride from conventional toothpastes is lost in the first few minutes after brushing. The formation of chemically stable fluorapatite, a component of tooth enamel, takes at least four hours. For improved health benefits, a formulation was needed that 'sticks' to the teeth and enables fluoride to be released slowly. Research at Queen Mary, led by the Institute of Dentistry's Prof. Hill, has shown that a toothpaste containing bioactive glasses can deliver this.

Hill specialises in understanding bioactive glasses and apatites and works closely with Dr. Gillam, a clinical dentist with expertise in managing dentine hypersensitivity. Their expertise, combined with those of researchers in Queen Mary's School of Engineering and Materials Science, has formed the interdisciplinary basis for this unique research on bioactive glasses. In REF 2014, Queen Mary submitted an impact case study focused on nano crystalline hydroxyapatite for toothpastes, while the current impact case study is on halogen containing glasses. Therefore, the current impact case study is not a continuation of the 2014 submission.

Bioactive glasses dissolve in body fluids such as saliva. Drawing on a detailed understanding of their structure and properties [3.1-3.4], Hill's team has developed 'smart' bioactive glass formulations that release calcium, phosphate and fluoride ions – in clinically relevant pH conditions – to form fluorapatite minerals, protecting the teeth from decay and reducing sensitivity.

Using fluorine-19 solid-state nuclear magnetic resonance spectroscopy (^{19}F NMR), the team has developed an analytical technique to identify fluorine-containing compounds. ^{19}F NMR is the only way that fluorapatite can be distinguished conclusively from the more soluble mineral hydroxyapatite, which is more susceptible to decay. The balance of minerals to form beneficial fluorapatites is delicate – in a key development, the researchers used ^{19}F NMR to show that there

is a critical concentration of fluoride in solution of 12 parts per million, above which undesirable calcium fluoride forms on enamel, and below which the beneficial fluorapatite mineral crystallises [3.5]. This phenomena is seen in the team's fluoride-containing bioactive glasses. Where the glass contains <5 mole% fluorine it forms fluorapatite [3.3, 3.4].

The group has shown that the new fluoride-containing bioactive glasses release calcium phosphate and fluoride over 12 hours, the average time between tooth brushing [3.3]. They have also shown that the rapid formation of fluorapatite happens in clinically relevant conditions. A healthy mouth has a neutral pH of around 7. Where the mouth is more acidic, the enamel on teeth begins to demineralize, putting them at risk of dental caries. This happens at around pH5. The bioactive glasses developed by the team dissolve almost 10 times faster at pH5 than at pH7. In effect, when faced with an environment that threatens caries, the 'smart' bioactive glasses respond, delivering fluoride, calcium and phosphate, helping to protect the teeth and raise the pH.

In further research, the group has investigated the ability of the glasses to block exposed dentinal tubules (microscopic channels in the teeth), which are associated with dentinal hypersensitivity. The group showed that the glasses reduced fluid flow through the dentinal tubules [3.6]. It is this fluid flow that causes tooth pain and sensitivity associated with hot or cold, or mechanical stimulation. Occlusion of tubules with apatite minerals (see Image 1 below), may prevent bacteria entering the dentine, reducing tooth decay. The group has also shown that the new toothpaste containing the bioactive glasses remineralises enamel at more than twice the rate of other leading toothpastes and remineralisation treatments [3.7]. Furthermore, the group has investigated the abrasivity of the bioactive glasses [3.8], studying the effects of particle shape and size on tooth enamel. This has enabled them to design a low-abrasivity toothpaste.

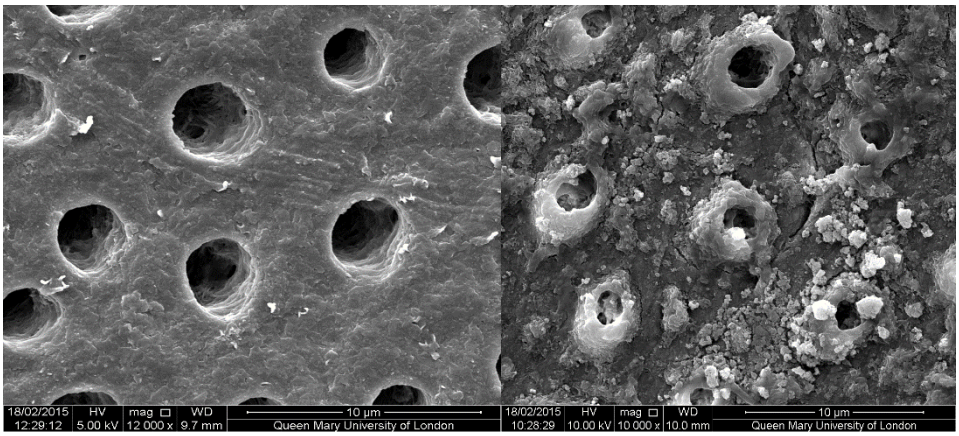

Image 1: Scanning electron micrgraphs of dentinal tubules: left, before treatment showing exposed tubules and right, after treatment with BioMinF and immersion in saliva.

3. References to the research

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[3.6] Shaikh, K., Pereira, R., Gillam D. G. & Phad, S. (2018). Comparative Evaluation of Desensitizing Dentifrices containing BioMin®, Novamin® and Fluoride on Dentinal Tubule

Occlusion before and after a Citric Acid Challenge – A scanning Electron Microscope *in-vitro* Study. *Journal of Odontology*, 2 (1), 1000105.
[3.7] Bakry, A. S., Abbassy, M. A., Alharkan, H. F., Basuhail, S., Al-Ghamdi, K. & Hill, R. G. (2018). A Novel Fluoride Containing Bioactive Glass Paste is Capable of Re-Mineralizing Early Caries Lesions. *Materials*, *11* (9), 1636. https://doi.org/10.3390/ma11091636
[3.8] Mahmood, A., Mneimne, M., Zou, L., Hill, R. G. & Gillam, D. G. (2014). Abrasive wear of enamel by bioactive glass-based toothpastes. *American Journal of Dentistry*, *27*, 263-267.

Evidence of quality of research:
[EQR.1] BioMinF. (2013). Venture Prize. The novelty and commercial potential of the new bioactive glass toothpastes was recognised with the award of the Venture Prize in June 2013. *Armourers and Brasiers, a Guild of the City of London*. The award was judged by three fellows of the Royal Society and three business experts and is based on the scientific innovation and commercial potential of the product and the business plan. GBP25,000.
https://www.armourershall.co.uk/venture-prize/previous-venture-prize-winners
[EQR.2] BioMinF. (2017). Finalist, Innovation of the Year. *Dental Industry Awards*. The scheme recognises excellence among the companies that support dentistry. The awards are a celebration of the high-quality work done by the dental industry, rewarding excellence in innovation and customer service and marketing.
https://www.dentistry.co.uk/2017/10/27/finalists-announced-dental-industry-awards/

4. Details of the impact

In 2014, Queen Mary set up BioMin Technologies Ltd, co-founded by Prof. Hill and Dr. Gillam, to develop a remineralising sensitivity toothpaste, BioMinF®. Launched in 2016, BioMinF contains unique bioactive glasses that dissolve in saliva to slowly release calcium, phosphate and fluoride into the mouth over 10-12 hours. These glasses are based on patents WO2011/000866 and WO2011/161422, granted in the USA and Europe respectively. In November 2017, BioMin launched the fluorine-free chloride version, BioMinC®, based on the patent WO2014/154874 (currently under examination).

Commercialising materials research: establishing BioMin Technologies Ltd
Licensing option agreements on the original fluoride bioactive glass patent submitted by Queen Mary in 2010 generated around GBP50,000, covering the costs of the patent filing. In July 2014, the university set up BioMin Technologies Ltd, using GBP25,000 from the Armourers and Brasiers Venture Prize – which supports the commercialisation of materials science research – to produce the prototype of BioMinF toothpaste. The new toothpaste launched in April 2016.

Following the successful launch, BioMin raised a further GBP410,000 from investors. The company now generates revenue of over GBP500,000 per year and forecasted to develop at over 50% compound annual growth from three sources [5.1]:

- Sales of toothpaste to global distributors (95% of sales are exported as the UK holds only 3-4% of the international toothpaste market)
- Sale of bioactive glass to toothpaste manufacturers
- Licensing fees for bioactive glass manufacture.

The manufacturing process and its international commercial success
BioMin Technologies Ltd licences the manufacture of its bioactive glasses to Cera Dynamics Ltd (CDL), based in Stoke on Trent, UK. BioMin Technologies Ltd then sells the bioactive glass to Group Pharmaceuticals (GP), a manufacturing company based in Bangalore, India, who produce the toothpaste for BioMin as well as selling directly within the subcontinent.

The manufacture of bioactive glasses for BioMin represents around 10% of CDL's dental materials business. CDL employs five people as a result of the contract with BioMin. CDL generates GBP200,000-250,000 sales per year through the sale of bioactive glass material to GP. At GP, BioMin-related manufacturing forms around ~5-10% of their business, employing a product manager and four employees in manufacturing and packaging. GP makes around 90,000 tubes of BioMinF toothpaste per month. Of these, 30,000 are sold back to BioMin. The remaining 60,000 tubes are sold to the domestic Indian market, where they cost about GBP2 per tube. This

generates around GBP120,000 per month in sales for GP. GP does not advertise BioMin toothpastes directly, they sell to dentists and pharmacists, who then recommend the product to patients with sensitivity or demineralisation. 80% of sales, therefore, are to consumers with a problem either with sensitivity or demineralisation. Around 30-40% of purchases are repeat purchases.

Currently, around 1,000kg of BioMin glasses are produced each month, which equates to about 250,000 tubes of toothpaste per month or three million tubes per year. Licensing options are in place for the manufacture and distribution of BioMin toothpastes in China, US, Australia, Israel, Thailand and Switzerland. A licensing deal is also planned in Brazil, one of the largest markets for toothpaste in the developing world. A full list of distributors is on the BioMin website [5.1].

Licensing and sales of BioMinF toothpaste around the world

The current markets for BioMinF toothpaste and the year entered are listed below:

Year	Countries entered
2016	India, UK
2017	China, Germany, Iceland
2018	Australia, Canada, Czech, Hungary, Lithuania, Poland, Slovakia, Slovenia
2019	Belgium, Finland, Ireland, Netherlands, Spain, Switzerland, UAE, US
2020	France, Italy, Qatar

The approximate annual number of toothpaste sales by country are:

- **India**, **1,000,000 tubes:** sold by GP (as Elsenz) and by Abbot Laboratories (as Hydent Pro)
- **China, 100,000 tubes:** sold by Kwang Wang (as BioMinF). Medical device approval in China for treating dentine hypersensitivity was granted in 2020 following a large clinical trial
- **Europe, 150,000-200,000 tubes**: sold in the UK and Germany, online through Dental Shop and Amazon. Also sold in German, Polish, Baltic and Slovakian pharmacies. From April 2020, BioMinF® for Kids has been on sale in European markets. In May 2020 BioMinC and BioMinF received a CE mark [5.2]
- **North America, 20,000 tubes:** FDA 510(k) medical device approval has been granted for BioMinC in the US [5.3]. Licensing/distribution deals have also been signed by Dr Collins in the US and with Healthpulze in Canada for BioMinC. BioMinF is marketed by Dr Collins in the US as BioMin Restore Plus. BioMinF has also been granted FDA 510(k) medical device approval and was granted FDA approval for Rx (prescription) sales in 2020. It is the first fluoride toothpaste to receive such approval in the US
- **Gulf states, 3,000 tubes:** Dubai-based Al Multaqa Drugs & Pharmaceutical will sell BioMin toothpastes across the Gulf states of UAE, Saudi Arabia, Oman, Bahrain, Qatar and Kuwait.

Improving oral care through the slow release of fluoride

The fluorapatite formed by BioMinF protects teeth from decay and blocks microscopic channels that cause sensitivity (see Image 1 above). Existing fluoride toothpastes use soluble sources of fluoride that are washed away by salivary flow and consequently higher concentrations of fluoride have to be used. The bioactive glasses developed by Hill and his team stick to the teeth and slowly deliver fluoride, providing a more effective delivery system. The key benefits of BioMinF toothpastes are:

- Controlled delivery of fluoride over time and responsive to clinically relevant pH conditions (the 5µm particles adhere to tooth surface and are less likely to be rinsed away by saliva)
- Enhanced acid resistance of fluorapatite over hydroxyapatite (a component of tooth enamel)
- Fluorapatite forms more rapidly.

Six independent clinical trials have shown BioMinF to be more effective than other leading sensitivity toothpastes, including GSK's NovaMin-based toothpaste and Colgate's Pro-Relief. BioMinF is more effective than both potassium nitrate and oxalate-based toothpastes in treating dentine hypersensitivity [5.4, 5.5]. When compared with the sodium fluoride toothpaste by Colgate for children aged 3-6 years, BioMinF was found to have higher salivary retention at one hour [5.1].

In addition, BioMinF is the first toothpaste to be accredited for both dentine hypersensitivity and tooth remineralisation by the Oral Health Foundation after a review by dental experts [5.6].

Recognition from medical professionals and users

The BioMinF toothpaste has received positive feedback from dental professionals. Sam Davidson, a hygienist in four practices across South East England, said, "I am now passionate about BioMin toothpaste. I trialled it on myself first. I found I was sensitive to cold air when I had had whitening treatment, so I used BioMinF for 14 days and the sensitivity was improved enough for me to go on with the treatment. As a trial in the practice, I gave about 30 patients a sample and all gave positive feedback. Many have continued to buy it" [5.7]. A dentist in India, Dr. Aggarwal, found that BioMin toothpastes had long-lasting beneficial effects. He said, "With the other toothpastes we found that just a few days after discontinuation of use the discomfort returned. Thus, we had a lot of patients complaining of rebound pain. With BioMin toothpastes the patient is getting more relief in the longer term" [5.1]. In 2019, BioMinF won the 'UK Best Oral Sensitivity Relief Provider' award in the Healthcare & Pharmaceutical Awards [5.8]. In 2019, Hill also became the first British scientist to win the American Ceramic Society's Varshneya Award for 'Glass Science with Impact' for his work on BioMinF [5.9].

BioMinF has been received positively by users too. From a survey of 436 users of the toothpaste, 52% said that it reduced their tooth sensitivity and 48% said that it was more effective than other sensitivity toothpastes they had tried. Users also found the texture (63%), foaming (86%), flavour (87%) and price (72%) of the toothpaste acceptable [5.10]. In April 2020, BioMinF toothpastes featured in BBC Four (weekly reach: 9,854,000) documentary 'How to Make', watched by over 300,000 people [5.11]. This generated significant interest in the toothpastes and the materials science behind them. Within two hours of the documentary, more than 2,000 people visited the BioMin website to find out more and proceeded to buy the toothpaste online.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] Fresh Perspectiv (2020). *Impact Case Study: Bioactive Glass Based Products - BioMin™*.
[5.2] The National Standards Authority of Ireland as a duly designated Notified Body for the purposes of the European Communities (Medical Devices) Regulations. (13 May 2020). *Quality System Approval* (GMDN Code: 11168 – BioMinC and BioMinF).
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[5.4] Pradeep, A. R. & Sharma, A. (2010). Comparison of clinical efficacy of a dentifrice containing calcium sodium phosphosilicate to a dentifrice containing potassium nitrate and to a placebo on dentinal hypersensitivity: a randomized clinical trial. *Journal of Periodontology*, *81* (8), 1167-1173. https://doi.org/10.1902/jop.2010.100056
[5.5] Ashwini, S., Swatika, K. & Kamala, D. N. (2018). Comparative evaluation of desensitizing efficacy of dentifrice containing 5% fluoro calcium phosphosilicate versus 5% calcium sodium phosphosilicate: A randomized controlled clinical trial. *Contemporary Clinical Dentistry*, *9* (3), 330-336. doi:10.4103/ccd.ccd_735_17
[5.6] Oral Health Foundation (2019). *Accreditation from expert panel for sensitivity and tooth remineralisation*. https://www.dentalhealth.org/news/oral-health-foundation-approves-biomin-toothpaste
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