

Institution: Queen's University Belfast		
Unit of Assessment: UoA3		
Title of case study: A New Product Range for the treatment of Bovine Digital Dermatitis and Related Topical Infections		
Period when the underpinning research was undertaken: 2000 to 2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Professor David Jones	Role(s) (e.g. job title): Pro-Vice-Chancellor, Professor, School of Pharmacy	Period(s) employed by submitting HEI: 1994-date
Period when the claimed impact occurred: 2013 - 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact		
<p>Digital dermatitis occurs extensively in cattle, with 70-95% of dairy herds showing symptoms and herd prevalence rates averaging between 20-30% in Europe and the USA. In the UK, at least 70% of herds are affected with about 41% of cattle having lesions. QUB research has led to the development of a suite of efficacious treatments that are now sold in three continents, with sales of more than GBP10,000,000, to date. Sales revenue has allowed the company to expand, building a second factory; this factory has been successfully audited by the FDA and is the only facility permitted outside the US to manufacture this range of products. The expansion has also allowed the company to employ 6 new staff.</p>		
2. Underpinning research		
<p>Digital dermatitis, a condition that presents as wart-type lesions on the heel of affected animals, adversely affects animal welfare, production and farm profitability. Treatment of digital dermatitis is compromised by a number of factors, notably, the short contact time between the affected area and the treatment (typically foot-baths), the high degree of keratinisation of the lesion that protects against the action of antimicrobial agents and the presence of copious organic matter (derived from soil) that reduces the efficacy of treatments.</p> <p>As a result, no single formulation is sufficiently robust to offer high efficacy against all stages of the disease. Traditionally, solutions of copper sulphate or formalin have been used to treat this condition, with reported environmental concerns. To address this clinical challenge, Jones has developed and refined/modified a series of antimicrobial products ranging from: bioadhesive solutions for use in foot-baths, combined keratolytic and antimicrobial bioadhesive pastes with enhanced bioadhesive and tissue-penetrative properties and bioadhesive antimicrobial sprays that initially disinfect wounds around the hoof prior to forming a moisture-resistant polymeric barrier that resists the ingress of microorganisms. The antimicrobial properties of the products are facilitated through a synergistic interaction between organic acids and oils from natural sources whereas their efficacy is optimised through the design of the formulations, as detailed above. These innovative products avoid many of the concerns of traditional treatments and present new opportunities for the improved treatment of digital dermatitis (regardless of the stage) and related conditions.</p> <p>The underpinning research for this project in the School of Pharmacy originated from the work by Jones (Chair in Biomaterials Science) on bio(muco)adhesion and bioadhesive formulations, chemical eradication of microbial biofilms and polymeric films as dosage forms. The research that enabled the current platform technologies was synthesised from separate but complementary themes, the overriding principle being the enhancement of antimicrobial</p>		

activities of topical platforms using strategies that simultaneously offer prolonged contact of the antimicrobial agent at the site of infection and solvent mediated enhancement of antimicrobial properties.

A precursor to the work on digital dermatitis was the development of a system to deliver antibiotics into the periodontal cavity, where the challenges were (i) adhesion to a moist epithelial surface and (ii) retention of the delivery system in the presence of a continuous flow of aqueous exudate from the periodontal cavity. This research led to a range of publications [R1-R6] studying the fundamental properties of bioadhesive (mucoadhesive) polymer systems, including their rheological and mechanical properties, which were crucial to clinical performance. The work was further extended to the design of moisture-activated bioadhesive platforms (polymeric systems that only become adhesive following absorption of water) designed as implants and/or drug delivery systems and bioactive film systems [R1-R6].

The experience gained from research on periodontal disease and bioadhesion proved highly relevant to a similar problem of retention of antimicrobial agents at the site of infection in digital dermatitis, a problem compounded by the presence of the infection on the underside of the hoof, the moist environment of the hoof and the removal of the formulation through normal ambulation. Effective adhesion to a wet surface under these conditions is particularly challenging, frequently resulting in poor product performance. Conventional adhesives (e.g. pressure-sensitive adhesives) are unsuitable for damaged skin and typically fail in a wet environment. If over-wetted (e.g., in situations where the surface is continually moistened by a flow of aqueous fluid), bioadhesives can lose adhesion as a slippery mucilage is formed.

Thus, seeking to overcome these challenges, three Knowledge Transfer Partnership schemes were successfully obtained by Provita Eurotech Ltd., a leading UK manufacturer of natural veterinary products, with Jones in the School of Pharmacy. These were then followed by direct project grant funding of the work of Jones. These collaborations, between 1997 and 2020, were worth approximately GBP929,000 in research funding and developed the current range of products, namely Hoofsure™ (an antimicrobial hoof-bath for cattle), Hoofsure Endurance™ (an antimicrobial foot bath for cattle with a more rapid antimicrobial activity and prolonged retention of antimicrobial agent on the hoof), Konquest™ (a bioadhesive paste that provides prolonged retention at and controlled delivery of antimicrobial and keratinolytic agents to the wart lesion) and Combat™ (an antimicrobial, polymeric film forming bandage designed to provide rapid disinfection and subsequent sealing of a wound to prevent reinfection). Whilst the products above were developed and released commercially before 2013 through research funding of GBP279,041, activities within **this current period** have been extensive and have been financially supported by Provita (**GBP649,874**). These have focused on agile formulation development resulting in new and second and third generation products designed for the treatment of digital dermatitis and related conditions. Activities have all been triggered by market research, clinical needs and feedback from practitioners.

3. References to the research

R1. JONES, D.S., IRWIN, C.R., BROWN, A.F., WOOLFSON, A.D., COULTER, W.A. & McCLELLAND, C. 2000. Design, characterisation and preliminary clinical evaluation of a syringeable, mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. *Journal of Controlled Release* **67** 357–368. [https://doi.org/10.1016/S0168-3659\(00\)00231-5](https://doi.org/10.1016/S0168-3659(00)00231-5)

R2. JONES, D.S., BROWN, A.F., WOOLFSON, A.D., DENNIS, A., MATCHETT, L.J. & BELL, S.E.J. 2000. Examination of the Physical State of Chlorhexidine Within Viscoelastic, Bioadhesive Semisolids Using Raman Spectroscopy. *Journal of Pharmaceutical Sciences* **89** 563 - 571. [https://doi.org/10.1002/\(SICI\)1520-6017\(200005\)89:5%3C563::AID-JPS1%3E3.0.CO;2-Q](https://doi.org/10.1002/(SICI)1520-6017(200005)89:5%3C563::AID-JPS1%3E3.0.CO;2-Q)

R3. JONES, D.S., BROWN, A.F. & WOOLFSON, A.D. 2001. Rheological characterisation of bioadhesive, anti-microbial, semi-solids designed for the treatment of periodontal diseases: Transient and dynamic viscoelastic and continuous shear analysis. *Journal of Pharmaceutical Sciences* **90** 1978 – 1990. <https://doi.org/10.1002/jps.1149>

R4. JONES, D.S., MULDOON, B.C.O., WOOLFSON, A.D. & SANDERSON, F.D. 2007. An examination of the rheological and mucoadhesive properties of poly(acrylic acid) organogels designed as platforms for local drug delivery to the oral cavity. *Journal of Pharmaceutical Sciences* 96 2632-2646. <https://doi.org/10.1002/jps.20771>

R5. ANDREWS, G. and JONES, D., 2006. Rheological characterization of bioadhesive binary polymeric systems designed as platforms for drug delivery implants. *Biomacromolecules*, 7 899-906. <https://doi.org/10.1021/bm050620y>

R6. JONES, D.S, LAVERTY, T. & ANDREWS, G.P. 2016. Statistical Modelling of the Rheological and Mucoadhesive Properties of Aqueous Poly(methylvinylether-co-maleic acid) aqueous networks: Redefining biomedical applications and the relationship between viscoelasticity and mucoadhesion. *Colloids and Surfaces: Biointerfaces*, 144, 125-134. <https://doi.org/10.1016/j.colsurfb.2016.03.008>

Grant Awards (KTP Schemes and Direct Project Funding with Provita Eurotech Ltd)

(i) 1997-2000: £82,010 (ii) 2000-2003: £87,010 (iii) 2008-11: £110,021 (v) 2014-2019: £649,874

4. Details of the impact

Research at Queen's in collaboration with Provita Eurotech Ltd. has helped to address the economic challenge associated with digital dermatitis as well as generating a commercial impact for the company. Provita Eurotech Ltd is an N Ireland based SME working in the animal healthcare sector, a market worth USD50,000,000,000 [S1]. The company has worked in partnership with the School of Pharmacy at QUB for **20 years, launching over 20 new products**. This has allowed the company to increase investment in R&D, and also to **expand the business infrastructure and employ an additional 6 staff**.

The Operations Director of Provita Eurotech Ltd highlights the importance of working with Prof Jones

"This twenty-year partnership under your academic leadership has revolutionised Provita Eurotech and has been instrumental in enhancing the size and international reputation of the company... Together we have identified opportunities earlier than our competitors, set out clear USP's and then worked in conjunction with you and your team to bring suitable products to market earlier than our competitors and in so doing have grown our business – a true partnership."

Impact on Product Development

A series of KTPs part funded by the Department for Enterprise Trade and Investment (DETI) and direct funding from the company led Jones and the company to develop novel bio-adhesive products to effectively prevent and control digital dermatitis. Unlike competitors, this product range offers a comprehensive prevention and treatment platform for digital dermatitis, independent of the stage of this condition.

Four of these products i.e. Hoofsure™, Hoofsure Endurance™, Konquest™ and Combat™ [S2] were launched commercially prior to 2013 but have had a major commercial impact within the current REF period (see below). Over the **last seven years, 8** new products have been successfully developed and launched; **10** existing products have been re-formulated either due to customer or regulatory requirements and a further **4** new products have been developed but not yet launched. These products have been marketed across **3 continents** (Europe, North America and Asia) and have led to Provita Eurotech Ltd becoming one of the world leading manufacturers of branded, sustainable products for this extremely challenging and prevalent animal health condition. As of October 2020, the footbath product has been used on over **41 million cow passes** [S1].

Provita
Animal Health Naturally

The Complete Hoofcare Range

A complete Hoofsure product range to optimize hoof health in dairy cattle

Footbath-it with **Endurance**
Spray-it with **Combat**
Wrap-it with **Konquest**

Special Hoofcare Offer
Buy 3 x 20 Litres Hoofsure Endurance
Get 1 Hoofsure Combat and
1 Hoofsure Konquest **FREE**

To claim this special offer or for further information contact Provita on
FREEPHONE 0800 3284982

Reduction of Lameness

Lameness is present in 70-95% of dairy herds with prevalence rates of 20-40% in Europe. Lameness in dairy cows can detrimentally affect many aspects of husbandry including reduced motility, reduced milk yield, reduced fertility and reduced feed intake, resulting in significant economic loss.

It is appreciated within the farming community that when digital dermatitis is detected on a given farm, it will not be possible to eradicate the disease completely; however, the company has shown that sustained levels of 5-10% lameness can be maintained when following the Provita protocol [S1].

This significant reduction not only addresses the welfare issue on the farm but also translates into huge cost savings, with lameness now the second largest economic loss on dairy farms.

A quote from a 90-herd dairy farmer demonstrates the benefit of using Hoofsure Endurance:

"I had struggled with digital dermatitis on my farm, and had tried many other products to control it however nothing seemed to control the problem effectively...By using Hoofsure Endurance within the plan and with the support of Provita, I'm saving money and the cows are in better form which means I'm in better form."[S3]

Commercial Impact

The main competitors for the footbath solution have been copper sulphate and formaldehyde. Both these chemicals had historically been considered effective as footbath options; however, copper sulphate has an extremely negative environmental impact and has now been banned from footbath use in Europe and formaldehyde has been classified as a Class 1B carcinogen. After development and launch of the Provita hoof bath product, two independent clinical efficacy studies were commissioned and completed within the current REF period. One was undertaken in the US [S4] and compared against copper sulphate (the market leader in the US) and the second was undertaken in the UK [S5] and compared to formaldehyde (the market leader in the UK). In both studies, the Provita footbath product outperformed the market leader in that territory in that it reduced lameness due to digital dermatitis further than the competitor.

A UK veterinary specialist stated that Hoofsure Endurance™ is:

"the only product I've ever trialled that has performed better than formalin, and I've trialled a lot of products"[S6].

Further to the publications, sales of the footbath product continued to grow and now collectively these products have generated in **excess of GBP10,000,000** [S1].

Increase in manufacturing capacity

Revenue resulting from the sales of the Hoofsure™ products have enabled Provita Eurotech Ltd. to develop a second site in Ireland where a new Supervisory Control and Data Acquisition (SCADA) - controlled high capacity manufacturing system has been installed. The manufacturing system has been designed to enable continuous manufacture and can process

up to **15,000,000 litres per year** which is predicted to meet the company's needs for at least 5 years.

"This relationship [with Queen's] has been instrumental in the success of Provita Eurotech through innovative product design, development of in vitro methodology to facilitate proof of concept, stability studies and development of manufacturing processes from pilot scale through to full scale manufacture: this included design and commissioning of a new manufacturing facility which has been successfully audited by FDA (the only facility permitted outside US to manufacture this range of products)." [S1]

5. Sources to corroborate the impact

S1) Testimonial from Provita Operations Director

S2) Provita website [Hoof Care – Cattle & Sheep | Provita Animal Health](#)

S3) Testimonials from farmer on efficacy of Hoofsure Endurance

S4) Smith AC, Wood CL, McQuerry KJ, Bewley JM. Effect of a tea tree oil and organic acid footbath solution on digital dermatitis in dairy cows. J Dairy Sci. 2014;97(4):2498-501. doi: 10.3168/jds.2013-6776. Epub 2014 Jan 31. PMID: 24485678

S5) Dyson S, Bell NJ. A quasi-randomised, non-inferiority clinical trial comparing Hoofsure Endurance with 4% formalin. Conference paper : 2014 Cattle Lameness Conference, 7 May 2014, Worcester, UK 2014 pp.69-70 ref.3

S6) Hoofsure brochure with quote from UK Veterinary Specialist