Institution: Queen's University Belfast

Unit of Assessment: UoA3

Title of case study: Vaginal rings to improve the sexual and reproductive health of women

Period when the underpinning research was undertaken: 2014–present

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s):	Period(s) employed by submitting HEI:
Prof. Karl Malcolm	Professor of Drug Delivery	1997–present
Dr. Peter Boyd	Senior Lecturer in Pharmaceutical Engineering	2014– present

Period when the claimed impact occurred: 2014–2020

Is this case study continued from a case study submitted in 2014? Y

1. Summary of the impact

QUB has been at the forefront of global efforts to develop products to protect women against sexually transmitted infection with human immunodeficiency virus (HIV). Supported by extensive research by Malcolm & Boyd over 17 years (including early development of the concept), a vaginal ring device offering sustained release of the antiretroviral drug dapivirine (Figure 1) has greatly impacted the direction and technology within the HIV prevention field. Phase 3 clinical trials were successfully completed in 2016, and a positive opinion from the European Medicines Agency was announced in July 2020. The ring will be the first woman-centered, long-acting HIV prevention method to reach market in 2022. Malcom & Boyd are also critical partners in the development of next-generation ring products offering increased breadth of HIV protection and hormonal contraception (Figure 2).

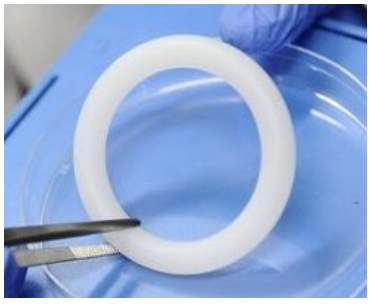

Figure 1. *Photo showing the dapivirine ring.*

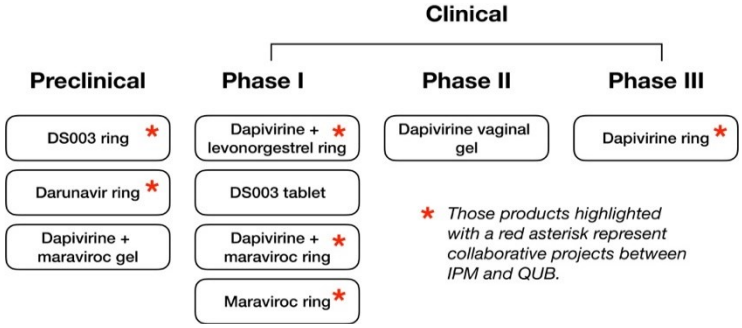

Figure 2. *International Partnership for Microbicides (IPM) current product portfolio, highlighting collaborative development projects with QUB.*

2. Underpinning research (indicative maximum 500 words)

HIV remains a leading threat to women's health and well-being worldwide. Despite global progress against the epidemic, HIV/AIDS remains the primary cause of death among women of reproductive age, and nearly 60% of new infections among adults in sub-Saharan Africa are in women. Young women in that region are three times more likely than young men to become infected with HIV. In the continued absence of an effective vaccine against HIV, researchers across the globe have focused on development of new biomedical strategies to reduce HIV acquisition rates.

Prior to 2000, vaginal rings had only been practically considered for release of steroid drugs for contraception and hormone replacement therapy. In 2003, Malcolm published two seminal papers, the first describing a vaginal ring for release of a then lead-candidate microbicide (nonoxynol-9), and the second describing the evaluation of the key physicochemical considerations for effective release of drugs from vaginal rings. Between 2005 and 2006, in collaboration with the International Partnership for Microbicides (IPM; a US-based non-profit product development partnership established in 2002), Malcolm demonstrated for the first time that a potent small-molecule antiretroviral drug – TMC120 (now known as dapivirine) – could be continuously released for many months from a silicone elastomer reservoir-type vaginal ring in quantities likely to provide protection against HIV transmission. Since then, QUB researchers Karl Malcolm, Peter Boyd (and previously David Woolfson) have partnered closely with IPM to further develop the dapivirine ring technology and other innovative sexual and reproductive health technologies for women (Figure 2). At the time of REF2014, the dapivirine ring had progressed as far as Phase 2 clinical studies.

Since 2014, several major advances have been made.

Table 1. *Table taken from Devlin et al., 2013 (a review article drafted by IPM) highlighting the role of QUB in development of the dapivirine ring.*

Vaginal ring prototypes.

Ring 001	• Developed in collaboration with the Population Council and QPharma. • Cured silicone consisting of two reservoir cores in a controlled release outer sheath. • 200 mg of dapivirine distributed between two reservoir cores.
Ring 002	• Developed in collaboration with Warner Chilcott • Reservoir ring system • Single reservoir containing 25 mg dapivirine • Excipients similar to Femring® and Menoring®
Ring 003	• Developed in collaboration with Warner Chilcott o Matrix ring system (dapivirine dispersed throughout silicone matrix versus API-containing cores inserted into ring reservoirs) o 25 mg dapivirine o Excipients similar to Femring and Menoring o Silicone curing: tin-catalyzed condensation reaction
Ring 004	• Developed by Queen's University Belfast and IPM • Matrix ring system • 25 mg dapivirine • Excipients similar to Estring® • Silicone curing: platinum-catalyzed hydrosilylation reaction
Placebo ring	• Developed by Queen's University Belfast and IPM • Matrix ring system • No API, contains titanium dioxide as colorant • Excipients similar to estring • Silicone curing: platinumcatalyzed hydrosilylation reaction

(i) The dapivirine ring: This ring product was originally developed by Malcolm and Janssen Pharmaceuticals in 2003, and then further developed in a partnership between QUB and IPM over more than 16 years (Table 1). Malcolm and Boyd have supported all aspects of formulation development and testing, including numerous patent applications **[R1,R2,R3]**, development and technology transfer of ring manufacturing methods, *in vitro* release testing **[R4]**, testing of polymorphic forms of dapivirine **[R4]**, development of a placebo ring for Phase 3 clinical testing, solving of manufacturing and control (CMC) issues in scale up of clinical manufacture, development of mechanical testing procedures **[R5]**, modelling of dapivirine release from a ring under real-world conditions, responding to regulatory queries, etc. Aside from dozens of published journal articles and patents, QUB has drafted hundreds of scientific reports for IPM over the past 5 years in support of the development of the dapivirine ring and regulatory submissions to the EMA/FDA. An acknowledgement letter from the Executive Vice-President of Product Development at IPM is provided, highlighting the very significant input from the QUB team **[S1]**.

In 2016, the results of two pivotal Phase 3 clinical studies testing dapivirine ring 'Ring 004' were reported **[S2, S3].** The ASPIRE Study and The Ring Study – involving 4,579 HIV-negative women from South Africa, Uganda, Malawi and Zimbabwe demonstrated that the ring reduced women's HIV risk by approximately 30% overall and was well-tolerated with long-term use. HIV risk was decreased by 45% among participants who used the ring at least some of the time, and by more than 60% among women 25 years of age or older who were highly adherent to the prescribed use regimen.

(ii) Combination antiretroviral rings: Successful development of the dapivirine ring has also spurred development of next-generation rings containing combinations of antiretroviral drugs. QUB and IPM are also at the forefront of these developments. A dapivirine + maraviroc ring completed Phase 2 clinical testing in 2014. A dapivirine + duranavir ring, a dapivirine+DS003 ring, and a novel dapivirine+5P12-RANTES ring are all currently in preclinical development.

(iii) Dapivirine + levonorgestrel MPT ring: One of the most significant developments in recent years has been the development of so-called multipurpose technology (MPT) vaginal ring products which simultaneously target prevention of HIV and unwanted pregnancy. Once again, QUB and IPM lead global development of these products, with a dapivirine + levonorgestrel ring currently in Phase 1 clinical testing (MTN-044/IPM 053/CCTN 019 study). Several major technical and manufacturing hurdles were overcome by the QUB team to permit this product to progress to the clinic **[R6,R7]**, most notably the propensity for levonorgestrel to chemically react with the silicone elastomer material used to make the ring, such that no levonorgestrel release was achieved from the early ring prototypes. Rather than halting development of this ring product and exploring other formulation options, QUB were able to reduce levonorgestrel binding in the ring from 100% to ~2% by carefully controlling levonorgestrel particle size, optimizing manufacturing conditions, developing custom grades of silicone elastomer, and applying post-manufacturing treatments **[R6]**. This issue of drug binding in silicone elastomer systems has since been observed by other pharmaceutical companies, who now routinely apply the solutions developed by QUB to overcome this problem. Furthermore, based on these findings, several global silicone elastomer suppliers are now working to reformulate their drug delivery materials to help reduce drug binding.

3. References to the research

R1) Malcolm, K., Woolfson, D., Romano, D. Platinum-catalysed intravaginal rings, US8580294 B2, 2016.
R2) Blanda, W., Holt, J.D., Brimer, A.N., Malcolm, K., McCoy, C., Murphy, D., Boyd, P.J.J Platinum-catalyzed silicone drug delivery devices and methods of use thereof, WO2016065096A1, 2016.
R3) Devlin, B., Holt, J.D., Brimer, A.N., Nuttall, J.P., Malcolm, K., Fetherston, S.M., Boyd, P.J.J. Combination Therapy Intravaginal Rings, US 2015/0136143 A1, 2015.
R4) McCoy, C.F., Murphy, D.J., Boyd, P., Derrick, T., Spence, P., Devlin, B., Malcolm, R.K. Packing polymorphism of dapivirine and its impact on the performance of a dapivirine-releasing silicone elastomer vaginal ring, J. Pharm. Sci. 106 (2017) 2015–2025. doi:10.1016/j.xphs.2017.04.026.
R5) McCoy, C.F., Millar, B.G., Murphy, D.J., Blanda, W., Hansraj, B., Devlin, B., Malcolm, R.K., Boyd, P. Mechanical testing methods for drug-releasing vaginal rings. Int J Pharm. 2019;559:182–191. doi:10.1016/j.ijpharm.2019.01.026
R6) Murphy, D.J., Boyd, P., McCoy, C.F., Kumar, S., Holt, J.D.S., Blanda, W., Brimer, A.N., Malcolm, R.K. Controlling levonorgestrel binding and release in a multi-purpose prevention technology vaginal ring device, J. Control. Release. 226 (2016) 138–147. doi:10.1016/j.jconrel.2016.02.020.
R7) Boyd, P., Fetherston, S.M., McCoy, C.F., Major, I., Murphy, D.J., Kumar, S., Holt, J., Brimer, A., Blanda, W., Devlin, B., Malcolm, R.K. Matrix and reservoir-type multipurpose vaginal rings for controlled release of dapivirine and levonorgestrel, Int. J. Pharm. 511 (2016) 619–629. doi:10.1016/j.ijpharm.2016.07.051.

4. Details of the impact

Significant impact has been made in this area of research since the REF 2014. At that time, the dapivirine ring had just completed Phase 2 clinical testing and plans were in place to initiate Phase 3 clinical testing in 2016. In this new impact case study, further impact is seen in:

i. 17 years of continuous product development and transfer of research involving partnership between IPM and QUB (see attached testimonial from IPM **[S1]**) has dramatically changed the landscape around HIV prevention products, and particularly the need for sustained release/controlled release solutions that are female-controlled.

ii. In 2016, two pivotal Phase 3 clinical studies (The Ring Study and the ASPIRE Study) were successfully completed testing the dapivirine ring in 4,500 women across clinical trial sites in Malawi, South Africa, Uganda and Zimbabwe (https://www.ipmglobal.org/our-work/our-products/dapivirine-ring) **[S2,S3]**. These were the first Phase 3 studies for a microbicide-

releasing vaginal ring device and have established the clinical resource for the testing of future HIV microbicide products.

iii. Successful completion of two open-label Phase IIIB clinical studies (950 women in the DREAM study **[S4]** and 1,500 women in the HOPE study **[S5]**) to provide the dapivirine ring to former ASPIRE trial participants for one year and to gain insights into how women use the ring following demonstration of its usefulness in reducing rates of HIV infection. Now completed, these studies demonstrated reduction in HIV risk of 63% and 39% respectively, no safety concerns, and a majority of women wanting the ring being offered. Measures of adherence indicated that a majority of women did in fact use the ring to protect themselves against HIV.

iv. On the 24th July 2020, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CMPH) delivered a positive opinion on the dapivirine-releasing vaginal ring for HIV prevention under EU Medicines for all (EU-M4All), a mechanism that allows the committee to assess and give opinions on medicines that are intended for use in countries outside the European Union under Article 58 of Regulation (EC) No 726/2004 **[S6]**. Regulatory submissions are now in progress to the US FDA and the South African Health Products Regulatory Authority, with plans to submit further applications to other regulators in eastern and southern Africa where women face the highest HIV risk. IPM is working with a global network of government, donor, private and civil society partners to determine how the ring could best fit into HIV prevention programs and is preparing for rollout of the ring at an affordable cost.

The QUB-IPM partnership is currently developing several innovative second-generation vaginal ring products. These products, several of which have advanced to early-stage clinical testing, are summarized on the IPM website (https://www.ipmglobal.org/our-work/product-pipeline). Malcolm and Boyd are building on the dapivirine ring technology to develop a three-month ring offering simultaneous release of dapivirine and the contraceptive progestin levonorgestrel for simultaneous prevention of both HIV and unintended pregnancy. However, combining two drugs within a single pharmaceutical product is particularly challenging from a drug formulation perspective.

A major obstacle was encountered by QUB researchers in early 2015 in the dapivirine + levonorgestrel ring programme. Unexpectedly, prototype rings known to contain substantial quantities of levonorgestrel did not provide release of levonorgestrel under *in vitro* testing conditions. Malcolm and Boyd demonstrated that levonorgestrel had reacted and bonded with the silicone elastomer component of the vaginal ring during the high temperature manufacturing process. Since short injection moulding cycle times (< 2 min) are necessary for efficient and practical manufacture of vaginal rings at commercial scale, reducing the manufacture temperature while extending the cycle time was not a viable option. Based on detailed understanding of silicone elastomer vaginal ring technology, Malcolm & Boyd proposed an alternative solution. All marketed vaginal rings make use of micronized drug materials, i.e., the drug powder is milled to produce particles typically of ~10 microns or less. Malcolm & Boyd hypothesized that use of larger particle size levonorgestrel in the rings would reduce the rate at which levonorgestrel dissolved in the silicone elastomer, thereby reducing the rate of the levonorgestrel binding reaction. Subsequent experiments demonstrated unequivocally the utility of this approach **[S7]**. Furthermore, they proved that by also switching to alternative medical-grade silicone elastomers that cure at lower temperatures, the extent of levonorgestrel binding in the ring device could ultimately be reduced to less than 5% of the total levonorgestrel loading, which is within acceptable regulatory specifications for a commercial drug product. On the basis of these important discoveries and solutions, in April 2017 IPM and its clinical trial partner (the Microbicide Trials Network) initiated MTN-030/IPM 041, a Phase I trial of the dapivirine-contraceptive ring in the US. The trial assessed the safety and pharmacokinetics of the three-month dapivirine-contraceptive ring, as well as a three-month dapivirine-only ring, when used for 14 days in 24 healthy, HIV-negative women who are not pregnant. In October 2018, the trial found the dual-purpose ring to be well-tolerated, and encouraging drug levels were seen in blood and vaginal fluid. A second Phase I trial (again in the

US) began in 2018. MTN-044/IPM 053/CCTN 019 is assessing the multipurpose ring's safety and pharmacokinetics when used for 90 days in 24 healthy, HIV-negative women who are not pregnant. Results from both trials will inform the next steps for the ring's formulation.

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

1. Letter of Support from Executive Vice-President, Product Development at the International Partnership for Microbicides highlighting the role of Malcolm & Boyd in helping to develop the ring technology
2. Nel, A. et al., Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women, N. Engl. J. Med. 375 (2016) 2133–2143. [This paper describes the results of the one of the Phase III clinical studies conducted in Africa.]
3. Baeten, J.M. et al., Use of a vaginal ring containing dapivirine for HIV-1 prevention in women, N. Engl. J. Med. 375 (2016) 2121–2132. [This paper describes the results of the one of the Phase III clinical studies conducted in Africa.]
4. Nel, A. et al., Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study, The Lancet HIV, 8(2) (2021) e77–e86. doi:10.1016/S2352-3018(20)30300-3
5. Baeten, J. et al., Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. The Lancet HIV, 8(2) (2021) e87–e95. doi:10.1016/S2352-3018(20)30304-0
6. Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden; Opinion of the EMA's human medicines committee (CHM). 24 July 2020; https://www.ema.europa.eu/en/news/vaginal-ring-reduce-risk-hiv-infection-women-non-eu-countries-high-disease-burden
7. Murphy, D.J. et al., Controlling levonorgestrel binding and release in a multi-purpose prevention technology vaginal ring device, J. Control. Release. 226 (2016) 138–147. doi:10.1016/j.jconrel.2016.02.020.