Institution: Queen's University Belfast

Unit of Assessment: 3a Pharmacy

Title of case study: Protecting Women from HIV AIDS: Dapivirine Vaginal Ring HIV Microbicide

1. Summary of the impact (indicative maximum 100 words)

In sub-Saharan Africa, 22 million people live with HIV/AIDS. Annual mortality is 1.5 million and sexual transmission accounts for ~90% of new infections. Young women are disproportionately affected due to socio-cultural issues. Seeking to empower them with an urgently needed female-initiated protective method, Malcolm & Woolfson developed the first antiretroviral (AR) microbicide vaginal ring (VR), which provides slow, continuous release of dapivirine for long-lasting protection against vaginal HIV transmission. Consequently, global microbicide development strategies were transformed, with the focus shifted from immediate-use gels to long-acting VRs. In August 2012, the dapivirine VR commenced final stage (Phase III) clinical trials in Africa.

2. Underpinning research (indicative maximum 500 words)

Woolfson[1] (Chair in Pharmaceutics, School of Pharmacy QUB) contributed substantially to the development of a hormone replacement therapy VR product, marketed as Femring® in the USA by Warner Chilcott Inc., that provides controlled release (CR) of estrogen for three months from a single device. The ability of VR devices to provide long-term continuous drug release for up to one year, coupled with their ease of user insertion and removal, make them highly relevant to the field of HIV microbicides. In this context, microbicides are defined as compounds applied inside the vagina to protect against sexually transmitted infections (STIs), including HIV. In the continued absence of a viable HIV vaccine, development of a vaginal microbicide is widely acknowledged to be the most practical strategy for the prevention of sexual HIV transmission. Early microbicide formulation strategies focused on gel products, intended for administration a short time before each act of intercourse. However, these gel-based microbicide strategies continue to be hindered by low user acceptability and poor adherance, particularly in the developing world. By contrast, VRs overcome many of these obstacles, since they can (i) be used without the knowledge of the male partner, (ii) be worn continuously, thereby offering 'round-the-clock' protection, and (iii) offer significantly increased levels of user compliance and acceptability.

Malcolm (Chair in Drug Delivery, School of Pharmacy QUB) and Woolfson published the first study[2] describing release of a candidate microbicide from a VR in 2003, along with fundamental research describing injection moulding of VRs and drug release mechanisms [3-4]. These studies established predictive models for determining the optimal physicochemical characteristics (hydrophobicity, molecular weight, etc.) of drugs for effective release from VRs, enabling VR technology to be applied to newer AR compounds. Since then, Malcolm and Woolfson have published many further papers on this subject, plus several book chapters/reviews on VR delivery technologies and their potential application to HIV microbicide development.

With the clinical failure of early non-specific microbicide candidates, the International Partnership for Microbicides (IPM) was established in Washington DC as an international development agency to lead efforts in delivering an effective microbicide product. With financial backing from major governments in the developed world and other leading global health organisations, such as UK DFID, The Bill and Melinda Gates Foundation, and The Rockefeller Foundation, IPM focused attention on CR delivery of potent AR drugs. Malcolm and Woolfson received funding from IPM to develop a VR device releasing the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine (also referred to as TMC 120). The key papers resulting from this work were published in 2005[5] and, in more detail, late 2006[6]. IPM funding has continued to date, now totalling £1.8M and further supplemented by three major EU Framework programmes and NIH funding. This funding has established two dedicated IPM laboratories in the School of Pharmacy QUB for the development, manufacture and testing of microbicide VRs.

3. References to the research (indicative maximum of six references)

1. Woolfson, A. D., Elliott, G.R.E., Gilligan, Claire A. and Passmore, Clare M. Design of an intravaginal ring for the controlled delivery of 17beta-estradiol as its 3-acetate ester. *Journal of Controlled Release* 61. 319-328. 1999.
2. Malcolm K.; Woolfson D.; Russell J.; Andrews C. In vitro release of nonoxynol-9 from silicone matrix intravaginal rings *Journal of Controlled Release* 91. 355-364. 2003.
3. Malcolm R.K, Woolfson A.D., Russell J.A. Tallon, P., McAuley L,. Craig D.Q.M. Influence of silicone elastomer solubility and diffusivity on the in-vitro release of drugs from intravaginal rings. *Journal of Controlled Release* 90. 217-225. 2003.
4. Malcolm, RK, McCullagh, S, Woolfson, AD, M. Catney, M, Tallon, P. A dynamic mechanical method for determining the silicone elastomer solubility of drugs and pharmaceutical excipients in silicone intravaginal drug delivery rings. *Biomaterials*. 23. 3589-3594. 2002.
5. Malcolm, R. K., Woolfson, A. D., Toner, C. F., Morrow, R. J. and McCullagh, S. D. Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings. *Journal of Antimicrobial Chemotherapy* 56. 954–956. 2005.
6. Woolfson, A.D., Malcolm, R.K., Morrow, R.J., Toner, C.F., McCullagh, S.D. Intravaginal Ring Delivery of the Reverse Transcriptase Inhibitor TMC 120 as an HIV Microbicide. *International Journal of Pharmaceutics* 325. 82-89. 2006.

Research Grants (Malcom and Woolfson): Development of vaginal ring microbicides. International Partnership for Microbicides, Washington DC. £1.8M (four grants from 2004 -20012); EUFP7 Consortium on Combined HIV Microbicide Delivery (CHAARM), £263k (to QUB), 2010 -14 and EUFP6 European Microbicides Project (EMPRO), £122k (to QUB), 2004-8; NIH U19/Cornell Univ, USA, Vaginal microbicides, £370k to QUB, 2007-12.

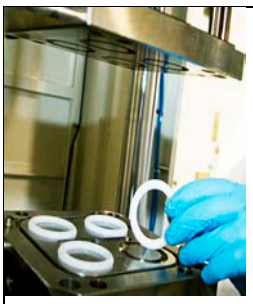
4. Details of the impact (indicative maximum 750 words)

In this case study, impact is seen in (i) transfer of the research from the laboratory to a global sponsor, (ii) a major shift in the sponsor's policy priorities for microbicide delivery (moving to a controlled release VR system that is coitally independent and away from immediate release, coitally dependent gel products), (iii) investment in successful Phase I and II trials, and a multi-million dollar investment in Phase III by both IPM and the US government (NIH), and (iv) use of the product by thousands of women enrolling in the trials for protection against HIV infection.

HIV/AIDS is the leading cause of death for women aged 15-44 worldwide, with most deaths occurring in sub-Saharan Africa. For physiological reasons, women are twice as likely than men to contract HIV from a single act of unprotected sex. However, societal and cultural prejudices mean that women are often highly dependent on male cooperation to protect themselves from infection.

Compared with other female-initiated microbicide strategies, vaginal ring products are widely acknowledged to offer the greatest potential. Their ability to be used covertly without the knowledge or co-operation of the male partner, the relatively high user acceptability[a] and the expectation of increased user adherence[b] in long-term use schedules suggest that a microbicide-releasing ring against HIV will challenge existing sexual norms within many developing world cultures by empowering women to take control of their own sexual health. Malcolm and Woolfson's work on VR microbicide delivery will provide women, for the first time, with a means of protecting themselves from heterosexually acquired HIV infection, without requiring support from the male partner. This is reflected in the change of direction from the key microbicide development agency, IPM, where £millions are now being invested in advanced trials (Phase III) of the first microbicide VR, developed by Malcolm and Woolfson, as a result of the impact of their technology on the microbicide field.

Following initial failings with the first generation non-specific anti-HIV compounds, microbicide research became focused on potent small molecule ARs similar to those used orally in Highly Active Anti-Retroviral Therapy (HAART). With this approach, a VR device must continuously



deliver an AR compound into the vaginal tissue over an extended time period in order to provide long-term protection. This required the pre-clinical development of an appropriate VR by Malcolm and Woolfson showing product performance characteristics (drug release, stability, durability, ease of manufacture) sufficient to justify the substantial financial commitment to take a product through clinical trials.

Malcolm and Woolfson served on IPM's first Scientific Advisory Board in 2004[c] and the group is currently listed as IPM's VR microbicide development partner[d]. The dapivirine-releasing VR developed by Malcolm and Woolfson has been adopted by IPM as its lead product, on the basis of its sustained drug release kinetics and excellent safety profile. IPM and its partners are funding a full clinical trials programme[e] for the dapivirine VR, as detailed below. Since 2008[f,g], three Phase I safety and availability clinical trials, IPM 001, 008 and 013 have been completed in Belgium. Also completed are a series of Phase II trials in HIV negative women. Trials IPM 001, 008 and 018 determined dapivirine concentrations in plasma and vaginal fluid samples, with safety assessed by pelvic/ colposcopic examinations, clinical laboratory tests, and adverse events. VRs were well tolerated with similar adverse events observed in the placebo and dapivirine groups. Dapivirine was successfully distributed throughout the lower genital tract at concentrations over 4 logs greater than the EC50 against wild-type HIV-1 (LAI) in MT4 cells. Mean plasma concentrations of dapivirine were < 50 pg/ml, an important observation since high systemic drug levels are undesirable in a vaginal microbicide due to the potential for development of resistance to the virus in infected users. **Based on these successful trials and related safety studies, the dapivirine VR developed by Malcolm and Woolfson has now entered into two major, multi-centre pivotal Phase III trials in Africa, which commenced in August 2012. These trials (described below) involve thousands of women In using the dapivirine VR as protection against heterosexually acquired HIV AIDS.**

Trial	Description	Countries	No*	Status
IPM 001	Dapivirine ring safety (Ring-001)	Belgium	12 women	Completed
IPM 008	Dapivirine ring safety (Ring-002)	Belgium	13 women	Completed
IPM 018	Dapivirine ring PK (Rings 002 & 003)	Belgium	24 women	Completed
IPM 011	Placebo ring safety & acceptability	South Africa Tanzania	170 women	Completed
IPM 024	Dapivirine ring PK (Ring-004)	Belgium	16 women	Completed
IPM 013	Dapivirine ring PK (Ring-004)	Belgium	48 women	Completed
IPM 015	Dapivirine ring safety (Ring-004)	Kenya Malawi South Africa Tanzania	280 women	Completed
IPM 027 (The Ring Study)	Dapivirine ring long-term safety and efficacy (Ring-004)	South Africa	1650 women	Ongoing

ASPIRE, also known as MTN-020, is a Phase III clinical study funded by the US National Institutes of Health through the Microbicides Trial Network (MTN). It seeks to determine safety and efficacy of the dapivirine VR for protecting against the sexual transmission of HIV when used by women for a month at a time. The study, which has started to enrol 3,476 women across several sites in Africa, will take approximately two years to conduct. Simultaneously, IPM's pivotal Phase III **RING STUDY** (IPM 027) is enrolling 1650 women. IPM have published a detailed 'Access Strategy' (May 2011)[h] for licensing andworldwide availability of the dapivirine VR, with these pivotal trials being key to final product registration. This trial information, involving substantial investment by IPM, demonstrates the outcome of the pre-clinical dapivirine VR research reported in 2005 and 2006 by Malcolm and Woolfson[i, j].

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

VR Acceptability studies

(a) Hardy E, Hebling EM, Sousa MH, Almeida AF, Amaral E, Delivery of microbicides to the vagina: difficulties reported with the use of three devices, adherence to use and preferences, *Contraception* 76.126-131. 2007. (DOI: 10.1016/j.contraception.2007.04.013)

(b) Ahrendt HJ, Nisand I, Bastianelli C, Gomez MA, Gemzell-Danielsson K, Urdl W, Karskov B, Oeyen L, Bitzer J, Page G, Milsom I. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 mu g of ethinyl estradiol and 3 mg of drospirenone Contraception 74. 451-457. 206.
(DOI: 10.1016/j.contraception.2006.07.004)

Malcolm and Woolfson: founding members of IPM's Scientific Advisory Board

(c) http://www.ipmglobal.org/publications/2004-ipm-annual-report page 23

QUB link to IPM as VR product development partner

(d) www.ipmglobal.org/our-partners/product-development-partners

Clinical trials on dapivirine VR microbicide

(e) www.ipmglobal.org/our-work/research/clinical-trial.

Paper (2009) detailing results from IPM 018 safety and pharmacokinetic study on QUB VR dapivirine ring, transferred to IPM for clinical development – paper links directly to References 5 and 6, Section 3.

(f) Nel A, Smythe S, Young K, Malcolm K, McCoy C, Rosenberg Z, Romano J . Safety and Pharmacokinetics of Dapivirine Delivery From Matrix and Reservoir Intravaginal Rings to HIV-Negative Women. *JAIDS-Journal of Acquired Immune Deficiency Syndromes* 51. 416-423. 2009.

Paper presenting data from Phase 1 trials IPM 001 and 008

(g) Romano J, Variano B, Coplan P, Van Roey J, Douville K, Temmerman M, Verstraelen H, Van Bortel L, Weyers S, Mitchnick M. Safety and Availability of Dapivirine (TMC120) Delivered from an Intravaginal Ring. *AIDS Research and Human Retroviruses* 25. 483-488. 2009.
(DOI: 10.1089/aid.2008.0184)

Global access strategy for dapivirine VR

(h) http://www.ipmglobal.org/publications/preparing-access-microbicides-and-dapivirine-ring-hiv-prevention-preliminary-strategy

(i) *Independent corroboration of the development of dapivirine VR by Malcolm and Woolfson and its subsequent clinical trial history*

Chair, Research and Advisory Steering Committee, International Partnership for Microbicides, Washington DC.

(j) Platinum-catalyzed intravaginal rings. US Patent Application 20120093911 claiming priority to US Provisional Application Serial No. 61/394,493, naming Malcolm and Woolfson as inventors of the dapivirine intravaginal ring, patent rights assigned by Queen's University to IPM to IPM.