Institution: University of East Anglia		
Unit of Assessment: 3 – Allied Health Professions, Dentistry, Nursing and Pharmacy		
Title of case study: Combating HIV through innovative medicine		
Period when the underpinning research was undertaken: 2005-2013		
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:**
Dr Sheng Qi	Reader	2005 - to present
Prof DQM Craig	Professor	2003 - 2013
Prof M Reading	Professor	2004 - 2010
Period when the claimed impact occurred: 2013 to 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Human immunodeficiency virus (HIV) infection is a devastating life-long disease that can lead to acquired immunodeficiency deficiency syndrome (AIDS). Globally, there are approximately 38,000,000 people living with HIV and approximately 24,500,000 people accessing life-saving antiretroviral therapy.

Research undertaken in the School of Pharmacy at UEA has had both **economic and health impact** through key input into the successful regulatory approvals of etravirine tablets (Intelence™). Specifically, UEA scientists used their material and formulation characterisation expertise to reveal the physical state of the drug in etravirine tablets and the underpinning mechanism of tablet stability. Since approval, this product has been prescribed to tens of thousands of patients each year, with global sales of EUR1,710,000,000 (03.2020) in the REF2021 period alone.

2. Underpinning research

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are a class of anti-HIV drug first developed in the 1990s. Resistance to the first generation of NNRTIs (e.g., nevirapine, efavirenz) developed rapidly. Etravirine was the first of a second generation of NNRTIs developed to combat drug resistant HIV. Etravirine is an extremely poorly soluble drug that proved to be highly challenging to be formulated into stable oral tablets that are well absorbed by the body.

Janssen, is a world-leading pharmaceutical company that joined the Johnson & Johnson family of companies in 1961. Janssen focus their innovation on six therapeutic areas, cardiovascular & metabolism, immunology, infectious diseases & vaccines, neuroscience, oncology, and pulmonary hypertension. They used a special formulation technology called solid dispersion technology for the delivery of etravirine. For solid dispersions, the physical state of the drug in the manufactured product plays a key role in the shelf-life stability of that product. Therefore, regulatory bodies require the pharmaceutical companies to use scientific data to demonstrate their clear understanding of this aspect of their product. With the research expertise in amorphous materials and solid dispersion technology of the UEA team [3.1-3.3], Janssen reached out to collaboratively prepare scientific evidence for their approval of Intelence™, the solid dispersion-based formulation of etravirine.

Research undertaken in the School of Pharmacy at UEA focussed on discovering and demonstrating the underpinning mechanism of the favourable shelf-life stability of etravirine oral tablet formulation. **Dr Sheng Qi** together with colleagues at UEA, produced a full mechanistic understanding of the stability of amorphous etravirine [3.4] which underpinned the stability data for Jansen's solid dispersion-based tablet formulations [3.5]. Using expertise in material science and characterisation they developed and applied the novel methodologies of differential scanning

calorimetry (DSC), modulated temperature differential scanning calorimetry (M-DSC), solid-state nuclear magnetic resonance (SS-NMR) and thermal-tip atomic force microscopy (AFM) to study the drug and its formulations. These analyses provided data and scientific insights which were not achievable by the conventional routine characterisation used in house at Janssen.

The research confirmed that Janssen's preferred formulation was homogeneous and stable without any separation between the drug and the polymer excipient; and released the drug at the desired efficiency upon administration. This collaboration generated three joint publications which were pivotal to Janssen securing USA and European regulatory approval for this novel HIV drug [3.4-3.6]. The third publication [3.6] modelled the release of poorly soluble drugs from solid dispersion formulation in the stomach and enriched the understanding of the working mechanism of this type of formulation that was used by Janssen in the marketed product.

3. References to the research

Underpinning research: The underpinning research outputs have all been published in competitive, international, peer-reviewed journals and form part of a larger body of such published work. Citation numbers are from Google Scholar (05/2/21)

(UEA authors in **bold**, Janssen and J&J authors underlined)

3.1 The development of microthermal analysis and photothermal microspectroscopy as novel approaches to drug-excipient compatibility studies.
Harding, L; Qi, S; Hill, G; Reading, M; Craig, DQM
(**2008**) *International Journal of Pharmaceutics*. Volume: 354 Issue: 1-2 Pages: 149-157. DOI: 10.1016/j.ijpharm.2007.11.009. Citations: 41

3.2 Characterisation of solid dispersions of paracetamol and EUDRAGIT I E prepared by hot-melt extrusion using thermal, microthermal and spectroscopic analysis.
Qi, S; Gryczke, A; **Belton, P; Craig, DQM.**
(**2008**) *International Journal of Pharmaceutics*. Volume: 354 Issue: 1-2 Pages: 158-167. DOI: 10.1016/j.ijpharm.2007.11.048. Citations: 147

3.3 An investigation into the effects of thermal history on the crystallisation behaviour of amorphous paracetamol.
Qi, S; Avalle, P; Saklatvala, R; **Craig, DQM**.
(**2008**) *European Journal of Pharmaceutics and Biopharmaceutics* Volume: 69 Issue: 1 Pages: 364-371. DOI: 10.1016/j.ejpb.2007.10.008. Citations: 77

3.4 An Investigation into the Crystallisation Behaviour of an Amorphous Cryomilled Pharmaceutical Material Above and Below the Glass Transition Temperature.
Qi, S; Weuts, I; De Cort, S; Stokbroekx, S; Leemans, R; **Reading, M**; **Belton, P**; **Craig, DQM**
(**2010**) *Journal of Pharmaceutical Sciences* Volume: 99 Issue: 1 Pages: 196-208. DOI: 10.1002/jps.21811. Citations: 63

3.5 Physicochemical Properties of the Amorphous Drug, Cast Films, and Spray Dried Powders to Predict Formulation Probability of Success for Solid Dispersions: Etravirine.
Weuts, I; Van Dycke, F; Voorspoels, J; De Cort, S; Stokbroekx, S; Leemans, R; Brewster, ME; Xu, DW; Segmuller, B; Turner, YTA; Roberts, CJ; Davies, MC; **Qi, S**; **Craig, DQM; Reading, M.**
(**2011**) *Journal of Pharmaceutical Sciences* Volume: 100 Issue: 1 Pages: 260-274. DOI: 10.1002/jps.22242. Citations: 105

3.6 Insights into the Role of Polymer-Surfactant Complexes in Drug Solubilisation/Stabilisation During Drug Release from Solid Dispersions.
Qi, S; Roser, S; Edler, KJ**; Pigliacelli, C; Rogerson, M;** Weuts, I; Van Dycke, F; Stokbroekx, S. (**2013**) *Pharmaceutical Research* Volume: 30 Issue: 1 Pages: 290-302. DOI: 10.1007/s11095-012-0873-7. Citations: 74

4. Details of the impact

The HIV virus is one of the new infectious agents which emerged in the 20th century with over 38,000,000 people living with HIV (1,800,000 being children) and over 690,000 people dying from an AIDS-related illness in 2019. The worst affected populations are disadvantaged communities living in Africa, Central and East Asia and Latin America. Currently UNAIDS is leading the global effort to end AIDS as a public health threat by 2030, as part of the Sustainable Development Goals, and as of the end of June 2020, 26,000,000 HIV patients were accessing antiretroviral therapy. However, the efficacy of the antiretroviral drugs is often not satisfactory. For example, worldwide resistance prevalence between 1996 and 2016 ranged from 12% to 22%.

This case study demonstrates impact arising from pharmaceutical research at UEA: **economic impact** both through direct product approval and sales, and **health impact** through clinical benefit to HIV patients.

Janssen is part of Johnson & Johnson and has more than 14,000 employees active in 100 countries and invests more than USD1,500,000,000 (12/2020) in research and development annually. The drug etravirine (marketed as Intelence™) was developed by Janssen for patients with drug resistant HIV. However, etravirine's poor water solubility required Janssen to use a special solid dispersion formulation technology, to ensure the good absorption of the drug when delivered by oral tablets. In order to obtain regulatory approval from the US Food and Drug Administration (FDA) for etravirine tablets, evidence for the physical state of etravirine in the manufactured tablets and the underpinning mechanism of tablet stability over its stated shelf-life was essential.

> *'Seeking expertise in drug formulation characterisation, Janssen approached UEA and Nottingham University to collaborate on the characterisation of this novel formulation. Work undertaken at UEA by Dr Sheng Qi and colleagues during the period of 2005 to 2008 developed a package of characterisation techniques to understand the molecular level organisation of the spray-dried etravirine formulation. Leveraging their expertise in the development and formation of molecular level dispersions, Dr Qi, and colleagues at UEA proved that etravirine was stably incorporated in the cellulose based carrier. These data explained and supported Janssen's in-house stability data on this product.'*
> [corroborating source 5.1]

The resulting data was part of the package submitted for FDA regulatory approval by Janssen. In 2008, etravirine became the first new NNRTI to be approved in over 10 years in the USA and Europe. The FDA approval states:

> *'Review of the drug product information resulted in several comments for the applicant. These primarily related to the spray-dried powder and tablet manufacturing processes. The applicant's responses to the comments have been found to be adequate'.*
> [corroborating source 5.2 page 11]

Subsequently etravirine was submitted for approval to the European Medicines Agency (EMA), with feedback stating:

> *'The active substance is well characterised and documented. It is a poorly soluble substance that has been formulated as a solid dispersion before tableting in order to overcome the solubility issues and to improve the bioavailability'*
> [corroborating source 5.3 page 7]

Economic impact

Marketed as Intelence™, etravirine was approved in 2008 for the treatment of adults carrying HIV strains resistant to other drugs. The favourable response from patients led to additional approval in 2012 for children aged 6 years or older. [corroborating sources 5.2 and 5.3].

Globally, first generation reverse transcriptase inhibitors and the newer NNRTIs are now the cornerstone of HIV therapy, accounting for USD12,800,000,000 in sales and 53% of all HIV

medication in 2015 [corroborating source 5.4].

Global sales of etravirine in the period 2014-2019 totalled EUR1,710,000,000 (03.2020) [corroborating source 5.5], a figure that does not include the provision of the drug at cost price through Janssen's Global Access Partnership Program (GAPP) in middle- and low-income countries or sales of generic etravirine manufactured through the granting of patents in China and India.

Health impact

The current WHO first-line HIV therapy for middle income countries is a cocktail of three anti-HIV drugs from two different classes which include NNRTIs such as etravirine [corroborating source 5.6]. Should first and second-line therapy be unsatisfactory, the WHO recommends third-line therapy with a minimal risk of cross-resistance to other HIV medicines.

Three drugs are specifically recommended for third-line therapy, among which etravirine is the only reverse transcriptase inhibitor. It is literally a life-saving medicine for patients in which the virus has acquired resistance to other anti-HIV drugs. The therapeutic and clinical impact of etravirine is not limited to its use as a mono-therapy drug. The clinical efficacies and cost-effectiveness when being used as a part of combination therapy with other anti-HIV agents have been evaluated and recognised by various clinical trials [corroborating sources 5.7 and 5.8] around the world. The magnitude and global reach of the positive health impacts have been articulated by a senior director from Janssen:

> *'Etravirine is now approved in over 100 countries around the world and has received additional regulatory approvals for use in children as young as 2 years old. It has been an instrumental tool in the armamentarium against HIV for more of 75 thousand HIV patients around the world. Janssen has also made the product available at low cost to middle and low-income countries and continues to donate the drug to HIV / AIDS charities. A partnership of J&J with New Horizons Collaborative has successfully increased access to HIV treatments for paediatric patients in Sub-Sahara Africa through charities such as the Elizabeth Glaser Paediatric AIDS Foundation.'* [corroborating source 5.1]

Broader applications and impact

Our collaboration with Janssen generated 3 scientific publications [3.4-3.6; Janssen / Johnson & Johnson authors underlined] which contribute to the understanding of solid dispersion technology and are highly cited by the wider pharmaceutical community who use the knowledge in product development of solid dispersions. This work was critical to the formulation of the marketed product. Up to today, there are more than 25 types of pharmaceutical oral products that are formulated using solid dispersions technology [corroborating source 5.9].

5. Sources to corroborate the impact

5.1 Testimonial letter from the Senior Director – CDTL and Preformulation Principal Scientist for Janssen R&D (24 Feb 2021)

5.2 FDA approval 2008 - Chemistry review downloaded from accessdata.fda.gov (accessed on 28.01.2021) and approval for treatment of children 6-18 years old in 2012 from page 17.

5.3 EMA approval 2008 – Assessment report for Intelence from ema.europa.eu (accessed on 28.01.2021) and approval for treatment of children 6-18 years old in 2012 from page 53.

5.4 Gubernick, SI; Félix, N; Lee, D; Xu, JJ; Hamad, B. The HIV therapy market. *Nature Reviews Drug Discovery* 2016, 15, 451-452; doi:10.1038/nrd.2016.69

5.5 Etravirine sales report from IQVIA, March 2020.

5.6 NIH Fact sheet - FDA Approved HIV Medicines: from aidsinfo.nih.gov (downloaded Jan 2021)

5.7 Jamie D Croxtall. Etravirine: a review of its use in the management of treatment-experienced patients with HIV-1 infection. *Drugs*, 2012 Apr 16, 72(6), 847-869.

5.8 Mauskopf, Josephine; Brogan, Anita J.; Talbird, Sandra E.; Martin, Silas. Cost-effectiveness of combination therapy with etravirine in treatment-experienced adults with HIV-1 infection. *AIDS*, 2012, 26(3), 355-364.

5.9 Phuong Tran, Yong-Chul Pyo, Dong-Hyun Kim, Sang-Eun Lee, Jin-Ki Kim, and Jeong-Sook Park. Overview of the Manufacturing Methods of Solid Dispersion Technology for Improving the Solubility of Poorly Water-Soluble Drugs and Application to Anticancer Drugs. *Pharmaceutics*, 2019, 11(3) 132