Institution: University of Nottingham

Unit of Assessment: UOA3 (Pharmacy)

Title of case study: Supporting regulatory approval of poorly soluble drugs for HIV and Hepatitis C

1. Summary of the impact

Research by the School of Pharmacy played a key role in the 2008 regulatory approval of Janssen Pharmaceutica's HIV drug Intelence®. As a poorly soluble drug, Intelence® required specialist formulation and was the first formulation of its type to be approved by the FDA and EMA. Intelence® offers significantly improved clinical outcomes due to its efficacy in patients with HIV resistance. Global Intelence® sales in 2012 were $349M, with additional not-for-profit supplies to resource-limited countries. As a result of this landmark regulatory approval formulation development strategies at Janssen were adapted enabling a further poorly soluble drug to reach the market. Telaprevir, a second-generation Hepatitis C treatment (marketed as Incivek®, Incivo® & Telavic®), gained global regulatory approval in 2011. 2012 sales exceeded $1bn in the US alone.

2. Underpinning research

The HIV drug TMC125 (etravirine) was developed by Tibotec (now Janssen Therapeutics) and manufactured by Janssen Pharmaceutica (both subsidiaries of Johnson & Johnson (J&J)). It is a poorly soluble drug requiring specialised formulation to enhance bioavailability. Following a number of formulation iterations Janssen found success by forming a solid dispersion of the drug via spray drying, and formulating a tablet with this spray-dried material. However, before etravirine no such formulation had reached regulatory approval and it was known that solid dispersions were difficult to reproducibly manufacture and potentially unstable. To satisfy US Food & Drug Administration (FDA) queries regarding spray dried powder characterisation, product stability and mechanism for improving bioavailability, Janssen required specialist expertise in nanoscale pharmaceutical analysis.

Research from the mid-90s onwards established Martyn Davies (Professor of Biomedical Surface Chemistry, University of Nottingham 1985-present), Clive Roberts (Professor of Pharmaceutical Nanotechnology, University of Nottingham 1990-present) and colleagues as world leaders in nanoscale and surface analytical strategies for pharmaceuticals. Their research focussed on developing new pharmaceutical applications of atomic force microscopy (AFM), nano/micro-thermal analysis (µTA), X-ray photoelectron spectroscopy (XPS) and secondary ion mass spectrometry (SIMS). This work contained a number of firsts in terms of nanoscale analysis of pharmaceuticals, including:

- discrimination of drug polymorphs by AFM (1) and µTA (2)
- real-time analysis by AFM of polymer degradation and release of an active agent (3)
- quantitative measurement of surface energy of pharmaceuticals by AFM (4)
- use of XPS and SIMS to characterize polymeric materials used in drug delivery (5)

Davies and Roberts used these methodologies to provide Janssen with critical understanding of the development of stable solid dispersions through an integrated postdoctoral research programme in collaboration with Prof Duncan Craig and Prof Mike Reading at UEA (2006-2008) (6,7). The research focussed on establishing a suitable solid dispersion methodology and formulation ratio of etravirine that would enable the drug to form and remain stable in a solid dispersion. Janssen provided various formulations of etravirine, produced via various methods (e.g. film casting, cryomilling, spray drying), with different drug loadings using a range of excipients (e.g. hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose, colloidal anhydrous silica and lactose monohydrate). Davies and Roberts exploited and refined advanced nano- and micro-scale analytical strategies (including the use of FT-IR, FT-Raman, TEM, XPS, SIMS and AFM) to provide structural and stability information on the formulation variants provided, with additional analysis using NMR and calorimetry performed at UEA. The results, particularly the visual information derived from TEM and AFM, were used to confirm structural characterisation of the preferred solid dispersion method (spray drying), determine a suitable excipient and stable range for drug loading (1.1 to 1.9 drug/HPMC) and provide insight into the *in vivo* behaviour and drug release mechanism of the formulation. Details of the non-confidential aspects of this work are

published (6). Based on the findings of the etravirine study, an optimal development strategy for solid dispersions has been developed at Janssen that includes a series of predictive screening experiments which probe physical stability (6).

3. References to the research

Key Papers (School of Pharmacy researchers in bold):

1. **Danesh A**, **Chen X**, **Davies MC**, **Roberts CJ**, **Sanders GHW**, **Tendler SJB**, **Williams PM** and Wilkins MJ. 2000. Polymorphic discrimination using atomic force microscopy: Distinguishing between two polymorphs of the drug cimetidine. *Langmuir* 16, 866-879. DOI: 10.1021/la990470a
2. **Sanders GHW, Roberts CJ, Danesh A**, Murray AJ, Price DM, **Davies MC, Tendler SJB** and Wilkins MJ. 2000. Discrimination of polymorphic forms of a drug product by localized thermal analysis. *Journal of Microscopy* 198, 77-81. DOI: 10.1046/j.1365-2818.2000.00709.x
3. **Shakesheff KM, Davies MC**, Heller J, **Roberts CJ, Tendler SJB** and **Williams PM**. 1995. Release of protein from a poly(ortho ester) film during surface erosion studied by in situ atomic force microscopy. *Langmuir* 11, 2547-2553. DOI: 10.1021/la00007a038
4. **Hooton JC**, German CS, **Allen S**, **Davies MC**, **Roberts CJ**, **Tendler SJB** and **Williams PM**. 2004. An AFM study of the effect of contact geometry and surface chemistry on the adhesion of pharmaceutical particles. *Pharmaceutical Research* 21, 953-961. DOI: **10.1023/B:PHAM.0000029283.47643.9c**
5. **Leadley SR**, **Davies MC**, Vert M, Braud C, Paul AJ**, Shard AG** and Watts JF. 1997. Probing the surface chemical structure of the novel biodegradable polymer poly(-malic acid) and its ester derivatives using ToF-SIMS and XPS. *Macromolecules* 30(22), 6920-6928. DOI: 10.1021/ma9702612
6. Weuts I, Van Dycke F, Voorspoels J, De Cort S, Stokbroekx S, Leemans R, Brewster ME, Xu D, Segmuller B, **Turner YTA**, **Roberts CJ**, **Davies MC**, Qi S, Craig DQM and Reading M. 2011. Physicochemical properties of the amorphous drug, cast films, and spray dried powders to predict formulation probability of success for solid dispersions: Etravirine. *Journal of Pharmaceutical Sciences* 100(1), 260–274. DOI: 10.1002/jps.22242

Grant Funding:

7. 2006-2008 Janssen/Tibotec: Nano analysis of solid dispersion formulations of TMC125. Davies MC, Roberts CJ £222,023 (Nottingham portion of grant).

4. Details of the impact

Janssen's HIV drug etravirine is a poorly soluble drug requiring specialised formulation. Davies and Roberts provided critical characterisation of the structure and stability of various etravirine formulations, supporting the regulatory approval of the resulting spray-dried solid dispersion tablet, the first formulation of its type to reach the market. Etravirine, marketed by Janssen as Intelence®, was the first Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) to be licensed in over 10 years and the first to show activity in people who had developed resistance to other HIV drugs. Subsequent updating of formulation development strategies at Janssen has led to a further spray-dried solid dispersion tablet formulation reaching the market, the Hepatitis C treatment telaprevir.

Janssen confirmed that the spray dried manufacturing route required "*significant optimisation and understanding to satisfy both our internal processes and external regulatory approval*" and that School of Pharmacy research (6) provided "*critical structural and stability information on various formulation variants of etravirine*" providing the regulatory bodies with "*evidence that we mechanistically understood the product*" (a). FDA approval of Intelence® was achieved in January 2008, with the Chemistry, Manufacturing and Controls review stating that "*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*". (b) EU approval was achieved later that same year. The European Medicines Agency (EMA) stated that "*spray drying was selected as the preferred manufacturing technique of etravirine solid dispersions. In addition, formulation studies have been performed to identify an adequate stabilizer for the active substance in solid dispersions*." and "*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". (c)

Global Phase III clinical trials in treatment experienced patients with evidence of NNRTI resistance (named DUET 1 and 2) confirmed that those treated with Intelence® had significantly better virological suppression at 24 weeks than those receiving placebo (d): 56 v. 39% in DUET 1 (patient numbers, n=612) and 62% vs. 44% in DUET 2 (n=591). An optional extension to the trial confirmed consistently higher sustained response rates with Intelence® at both 48 and 96 weeks (d). Prof Richard Haubrich of the University of California San Diego, an Investigator on the DEUT studies, said "*Etravirine breaks new ground in the NNRTI class, and provides a new option to thousands of treatment-experienced patients with NNRTI-resistant HIV*". (e) Following initial regulatory approval of 100mg tablets in 2008 and 200mg tablets in 2010, 25mg tablets were approved in 2012 coinciding with approval for use in children from 6 years (US (b) and EU (c)). Intelence® is only approved for treatment-experienced patients who have HIV strains that are resistant to an NNRTI and other HIV drugs. It is not approved for treatment naïve patients as further evidence is required to determine the benefits to this patient population. Global Intelence® sales were $349M in 2012 and sales for the first half of 2013 were $192M, up 12% from the first half of 2012 ($171M) (f).

In 2011 around 34 million people were living with HIV, however, the number dying of AIDS-related causes fell to 1.7 million, down 24% since 2005 (UNAIDS Global Fact Sheet, 2012). This is partly related to improved antiretroviral therapy. Such therapy is, however, being challenged by the emergence of viral resistance. Figures from the WHO show that in high-income countries (US, EU, Japan, Australia) 10-17% of treatment-naïve patients have resistance to at least one HIV drug, while estimates of HIV drug resistance in resource limited countries is around 6.6%, with resistance to NNRTIs the most common (WHO HIV Drug Resistance Report, 2012).

In 2009, the combination of Intelence® with two other drugs having activity against resistant HIV (raltegravir and darunavir) was trialled in heavily treatment experienced patients (n=103) with multidrug-resistant HIV. Results showed that 90% of patients had undetectable viral loads after 24 weeks and 86% after 48 weeks, similar to that expected in treatment naïve patients (g). This combination of drugs was subsequently endorsed as candidates for 3rd line therapy by the WHO in 2010, and in 2012 etravirine was further endorsed by the WHO, by being placed on their List of Prequalified Medicinal Products, which is used to guide UN agencies procurement (h).

Intelence® is one of three HIV drugs available via Janssen's Global Access Partnership Program (GAPP) through which Janssen are committed to helping people living with HIV in resource-limited settings by ensuring effective and sustainable access to their HIV medicines (i). Via GAPP regulatory filings are prioritised where there is public health need. Intelence® has gained regulatory approval in 28 countries (including South Africa, Thailand and Jamaica) with 9 additional filings pending (as of May 2013). Royalty-free licencing and distribution agreements help ensure rapid availability, supply, and medically appropriate use, along with a not-for-profit price. Our role in the regulatory approval of Intelence® has therefore led to global impact on health and welfare by significantly improving clinical outcomes for patients with drug resistant HIV.

Following the collaboration with Nottingham, Janssen confirmed that "*some of the methodologies used have been adapted and are now used at Janssen in developing similar formulations*" (a), including telaprevir, a new treatment for Hepatitis C virus (HCV) (a). Developed by Janssen in collaboration with Vertex Pharmaceuticals and Mitsubishi Tanabe Pharma (MTP), telaprevir gained regulatory approval in 2011, in the US (marketed by Vertex as Incivek®), in the EU (marketed by J&J as Incivo®) and in Japan (marketed by MTP as Telavic®) (j).

Latest figures from the WHO show that approx. 150 million people worldwide are chronically infected with HCV (WHO Hepatitis C Factsheet, 2012). Telaprevir is a second generation treatment for HCV genotype 1 (the most common genotype), which offers substantially better clinical outcomes than standard treatment alone. Combined results from three Phase III clinical trials (named ADVANCE, ILLUMINATE, REALIZE, overall n=2290 (e)) showed that sustained viral

response (viral cure) rates for telaprevir compared to standard treatment were: 79% vs. 46% for previously untreated patients; 84% vs. 22% for patients suffering a relapse; 61% vs. 15% for partial responders; and 31% vs. 5% for null responders. Treatment time in certain patients could also be halved to 24 weeks, compared to standard treatment. Following EMA approval, Charles Gore of the World Hepatitis Alliance said *"[This] is the first treatment breakthrough in more than 10 years and a significant step forward for the hepatitis C community*" (e). In its first full year on the market, telaprevir sales reached $1.16bn in the US alone (Incivek® sales and royalties from Incivo® made up 84% of Vertex's total revenue in 2012) (j). J&J have only highlighted Incivo® sales since January 2013, with current half year sales of $334M (f).

In summary, research carried out in the School of Pharmacy has enabled Janssen to overcome formulation issues associated with poorly soluble drugs and gain the first regulatory approvals of spray-dried solid dispersion tablet formulations, in the HIV drug Intelence® and the Hepatitis C drug telaprevir. These drugs both provide a step change in treatment options resulting in significantly improved clinical outcomes for patients and global impact on health and welfare. Global Intelence® sales were $349M in 2012, while telaprevir sales (as Incivek®) reached over $1bn in the US alone.

5. Sources to corroborate the impact

a. Corroborative Statement and email correspondence from the Vice President Drug Product Development, Janssen Pharmaceutica.(on file)
b. 2008 FDA approval of Intelence®, URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022187TOC.cfm (accessed 05/06/13) the CMC report (on file) is available via the "Chemistry Reviews" tab (quote taken from p11). 25mg dose approved in 2012 for treatment of children from 6 to 18 years, URL: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/022187s009ltr.pdf (accessed 05/06/13 – also on file).
c. 2008 EMA CHMP assessment report for Intelence®, URL: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000900/WC500034183.pdf (accessed 05/06/13 – also on file) (quotes taken from p 6 and 7). 25mg dose approved in 2012 for treatment of children from 6 to 18 years, URL: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000900/WC500134832.pdf (accessed 05/06/13 - also on file).
d. Etravirine Phase III clinical trials: DUET 1 – Madruga *et al*. *Lancet* 2007; 370: 29–38. DOI: 10.1016/S0140-6736(07)61047-2**;** DUET 2 – Lazzarin *et al*. *Lancet* 2007; 370: 39–48. DOI: 10.1016/S0140-6736(07)61048-4**;** and pooled results from DUET 1 and 2 at 96 weeks – Katlama *et al*. *Antiviral Therapy* 2010; 15: 1045-1052. DOI: 10.3851/IMP1662.
e. J&J Press releases (accessed 22/07/13 – also on file) - Intelence® regulatory approval, URL: http://www.investor.jnj.com/releasedetail.cfm?releaseid=288508; and Incivo® Phase III results and EMA approval, URL: http://www.investor.jnj.com/releasedetail.cfm?releaseid=606591
f. J&J financial reports, URL: www.investor.jnj.com/sales-earnings.cfm (accessed 05/06/13 – also on file) Intelence® sales highlighted from 2011 onwards and Incivo from 2013 onwards.
g. Trial results of combination of three HIV drugs with resistance activity: Yazdanpanah Y, *et al*. *Clinical Infectious Diseases* 2009; 49:1441–9. DOI: 10.1086/630210.
h. WHO endorsements of Intelence® - WHO Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach, 2010; URL: http://apps.who.int/iris/bitstream/10665/44379/1/9789241599764_eng.pdf (accessed 05/06/13 – also on file), data on 3rd line therapy is on p58. The WHO List of Prequalified Medicinal Products, URL: http://apps.who.int/prequal/ (accessed 05/06/13 – also on file), access to the full list is via the "Prequalified Medicines" quick link.
i. Janssen Global Access & Partnerships Program, URL: www.janssenrnd.com/our-caring/global-access (accessed 05/06/13 - also on file).
j. 2012 Financial report from Vertex Pharmaceuticals, URL (accessed 21/06/13 – also on file): http://investors.vrtx.com/releasedetail.cfm?ReleaseID=736569 also details regulatory approval and marketing information for telaprevir in US, EU and Japan.