Institution: University of Greenwich

Unit of Assessment: (UoA 8) - Chemistry

Title of case study: Managing risk associated with crystal polymorphism in pharmaceutical development

1. Summary of the impact

Nearly all solid dosage forms contain drugs in crystalline form; and all crystals have the potential to 'morph', suddenly, into different forms which can affect the safety and efficacy of the medicinal product. A number of high-profile cases in which marketed medicines had to be withdrawn [Lee, *et al.,* Annu. Rev. Chem. Biomol. Eng. 2011, **2**, 259-280] led multinational drug company Pfizer to conclude that a greater understanding of polymorphism was required to enable drug product design for the 21st Century. The University of Greenwich pioneered methods to predict crystal behaviour on the shelf and during manufacture that were affordable, timely and effective. It enabled Pfizer to select the optimal polymorphic drug form and manage risk associated with uncontrolled solid-state transformations, thereby safeguarding patients and avoiding huge costs.

2. Underpinning research

Polymorphism is a phenomenon where drug molecules can adopt multiple crystalline packing arrangements or conformations in the solid state. It affects manufacturing performance, the stability of formulated medicines and the extent of oral absorption and hence the dose. An optimal polymorphic drug form must be selected that is thermodynamically stable. Pfizer did not have the analytical tools to provide a deep knowledge of the emerging importance of polymorphism. Pfizer identified **Martin Snowden**, with expertise in surface and colloid chemistry, and **John Mitchell**, a physical organic chemist, to lead research to develop the technology in four areas. **Stephen Wicks,** Vice President of Pharmaceutical Science and Technology and UK Development Director at Pfizer, led the technology transfer project.

2.1 Production of highly pure crystals for physical and mechanical evaluation

Flash-Liquid Chromatography is a purification method of choice for preparative separations of drug molecules. Flash-LC had limited ability to produce pure fractions for routine solid-state characterisation because of its reliance on UV detection: important organic solvents used to achieve high purity levels had high UV cut-offs; many new drug candidates lacked significant chromophores. The Evaporative Light Scattering Detector (ELSD) was adapted for use with Flash-LC to allow the routine preparation of Active Pharmaceutical Ingredients (APIs) for materials science analysis when UV detection was not possible. [3.1.1 and 3.1.2]

2.2 Characterisation of crystal disorder to predict catastrophic solid-state transitions

Single-crystal X-ray diffraction produces a complete model of a material's molecular and solid-state structure. *Ab.initio* prediction of crystal structure is also possible. The practice was considered using a combination of structural information and structure prediction methodologies to develop powerful structure prediction procedures for drug crystals and more complex solid-state forms, e.g. salts. [3.2.1-3.2.3]

2.3 Prediction of processing properties of pharmaceutical powders using single crystals

Manufacturing processes can be problematic when drug crystals deform elastically in production machinery. Particle physics investigations required large quantities of pure, expensive crystalline drug. Consequently such studies were deferred to a point in the development programme where change, however desirable, was impractical. Indentation techniques were developed using highly

purified single crystals to investigate the processing performance of drug candidate crystals, very early in the development process, to provide the opportunity to engineer and substitute improved solid-state variants to avoid processing problems. [3.3.1-3.3.3]

2.4 Chemical imaging of pharmaceutical products

Conventional analytical techniques sample the average bulk characteristics of pharmaceutical products. It is possible to determine the total drug content in a tablet but not the distribution of particles within a matrix formed with other formulation excipients. With spatial and chemical information, obtained using near infrared and Raman spectroscopy, it is possible to generate chemical images of each ingredient within the formulation. The physicochemical form of drug, in the presence of excipient particles, in the sample can be determined along with the size of any material clustering and spatial position relative to other components. The interface with processing machinery can also be determined. This research increased process understanding and material attributes associated with the clinical performance of the product. [3.4.1-3.4.4]

3. References to the research (REF1 submitted staff in **bold,** **REF2 Outputs)

3.1.1 Mathews, B. T., Higginson, P. D., Lyons, R., **Mitchell, J. C.**, Sach, N. W., **Snowden, M. J.**, Taylor, M. R., & Wright, A.G. (2004). Improving Quantitative Measurements for the Evaporative Light Scattering Detector. *Chromatographia*, *60*(11-12), 625–633. http://dx.doi.org/10.1365/s10337-004-0441-3

3.1.2 Dubant, S., Mathews, B., Higginson, P., & Crook, R., **Snowden M.J., Mitchell, J.C., (2008). Practical solvent system selection for counter-current separation of pharmaceutical compounds. *Journal of Chromatography A*, *1207*(102), 190–192. http://dx.doi.org/10.1016/j.chroma.2008.08.113

3.2.1 Johnson, M. N., & Feeder, N. (2004). dl-Histidine dl-tartrate. *Acta Crystallographica Section E: Structure Reports Online*, *60*(7), 1273–1274. http://dx.doi.org/10.1107/S1600536804015296

3.2.2 Johnson, M. N., & Feeder, N. (2004). d-Histidinium (2S,3S)-tartrate. *Acta Crystallographica Section E: Structure Reports Online*, *60*(8), 1374–1375. http://dx.doi.org/10.1107/S1600536804017088

3.2.3 Johnson, M. N., Feeder, N., & **Snowden, M.J.** (2004). Effects of chirality on the salt formation of histidine. *Journal of Pharmacy and Pharmacology*, *56*(S1), 24–25. http://dx.doi.org/10.1211/002235704777489212

3.3.1 Taylor L. J., Papadopoulos D. G., Dunn P. J., Bentham A. C., Dawson N. J., **Mitchell J. C.** & **Snowden M. J**. (2004). Predictive milling of pharmaceutical materials using nanoindentation of single crystals*, Organic Process Research & Development*, *8(4)*, 675-679. http://dx.doi.org/10.1021/op0300241

3.3.2 Taylor L. J., Papadopoulos D. G., Dunn P. J., Bentham A. C., **Mitchell J. C**., & **Snowden M. J**. (2004), Mechanical characterisation of powders using nanoindentation, Powder Technology, 143-144, 179-185. http://dx.doi.org/10.1016/j.powtec.2004.04.012

3.3.3 Taylor L. J., Papadopoulos D. G., Dunn P. J., **Mitchell J. C.**, & **Snowden M. J.** (2004). Milling Made Easy: Nanoindentation as a predictor of bulk properties, *Pharmaceutical Technology Europe, 16(12)*, 51-54. http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=138086&sk=&date=&pageID=2

3.4.1 Šašić, S., Clark, D. A., **Mitchell, J. C.**, & **Snowden, M. J.** (2005). Raman line mapping as a fast method for analyzing pharmaceutical bead formulations. *Analyst*, *130*(11), 1530–1536.

http://dx.doi.org/10.1039/B506523B

3.4.2 Šašić, S., Clark D. A., **Mitchell, J. C**. and **Snowden M. J**., (2005). Analysing Raman images of pharmaceutical products by sample-sample 2D correlation, *Appl. Spec.*, **59**, (5), 630-638. http://dx.doi.org/10.1366/0003702053946047

3.4.3 Šašić, S., Clark, D. A., **Mitchell, J. C.**, & **Snowden, M. J.** (2004). A comparison of Raman chemical images produced by univariate and multivariate data processing—a simulation with an example from pharmaceutical practice. *Analyst*, *129*(11), 1001–1007. http://dx.doi.org/10.1039/B409879J

3.4.4 Brody, R.H., Kierstan, K.T.E., Clark, D.A., **Mitchell, J.C.** & **Snowden, M.J.** (2003). Analysis of challenging pharmaceutical samples using chemical and elemental images. *Microscopy and Microanalysis*, 9 (Suppl. 02), 1108-1109. http://journals.cambridge.org/article_S1431927603445546

4. Details of the impact

Nearly all solid medicines like tablets and capsules contain drugs in crystalline form; and all crystals have the potential to 'morph' into not one but many alternative forms. The likelihood of the crystals actually changing and becoming a danger to patients is very small but it can and does happen, with catastrophic consequences.

In 1988, a clinical failure of Tegretol (carbamazepine) tablets, the anticonvulsant widely used with epilepsy, was observed. It was believed to be caused by a phase conversion from the anhydrate to dehydrate form. In 1998 Abbott Laboratories withdrew Norvir (ritonavir), essential at that time in the treatment of HIV/AIDS, because the capsules unexpectedly failed dissolution tests. The public were without an essential drug while researchers investigated. They finally identified that the drug crystals had changed into a more stable, less soluble polymorph which contaminated laboratories and effectively halted production processes. They had to completely reformulate the drug and develop a new capsule product. The case cost Abbott hundreds of millions of dollars and over 600 scientists working for nearly a year to resolve the issue. The estimated loss in sales in 1998 alone is $250m.

Pfizer experienced similar problems with two drugs in development and concluded that a deeper scientific knowledge of polymorphism was an emerging need in the pharmaceutical industry. The consequences were typically catastrophic, hard to predict, clinically and economically unacceptable, and damaging to patients' trust in the company to produce the quality products they relied on.

Pfizer identified internal and external drivers for the need to understand polymorphism on a more scientifically rigorous basis. These drivers included:

- emphasis on the chemical rather than physical attributes of drugs and excipients;
- the instrumentation used to characterise polymorphism was relatively simplistic and unable to predict the potential for phase transition;
- the existing protocols to test physical performance required large quantities of expensive pure solid drug, and occurred too late in the development process to stimulate the re-engineering of defective crystalline drug forms;
- an industry-wide drive for more rapid drug development and clinical testing.

Pfizer turned to the University of Greenwich to develop the scientific methodology to:

- produce small quantities of highly purified drug crystals, alone and in drug product matrices, from side streams of conventional pilot batches;
- use the pure drugs to develop tests on single crystals, a process which is much cheaper and

can be performed at the start rather than end of the drug development process;
- develop tests that could predict polymorph instability and how they behave during manufacture, and in turn allow the engineering and understanding of new solid-state forms for development.

Since 2008 Pfizer has been able to apply the resulting methodologies, systematically to the development of crystalline APIs for use in solid oral and inhalation dosage forms. The company has also applied them to understand the risk for products licensed from other companies not using this scientific paradigm. Pfizer has invested £2.4m in the university to date. The programme has resulted in critical technology and human resource transfer to the company as well as 27 refereed publications. To date 24 researchers have progressed through the scheme; 40% have taken up posts within Pfizer and 42% with other leading pharmaceutical companies.

The larger impacts are that Pfizer has vastly reduced the risk of polymorphism in its drugs, increasing the confidence of patients and health professionals. Examples of what might have happened without the university's pioneering research abound, for instance to UCB with Parkinson's disease drug rotigotine. Filed in 2003 as a drug that did not exhibit polymorphism, rotigotine was delivered through Neupro skin patches and many patients experienced an improved quality of life. In 2008, dendritic structures were observed: a new form polymorph had crystallised which reduced the patches' efficacy. The product was withdrawn in the US in 2008 and did not return to the market until 2012. Similarly, in 2010 BMS withdrew 64 million Avalide tablets (hydrochlorthiazide and irbesartan) over concerns that irbesartan crystals had converted to a less soluble polymorph. Avalide sales were calculated to be $310 million in the first nine months of 2010. Pfizer is able to safeguard its patients and avoid the cost associated with recalls and the redevelopment and relaunch of clinically essential products.

5. Sources to corroborate the impact

5.1 ***Letter of Corroboration from Pfizer Inc.*** A corroborating letter is available from the R&D Director, Pfizer Ltd. The contact for communication the Senior Director and Head of Materials Science Pfizer Ltd.

5.2 ***Corroborating Pfizer Publications.*** The following publications, by Pfizer lead authors, confirm the application and development of the tools and techniques developed by the Pfizer-University of Greenwich partnership.

5.2.1. *Extracting process-related information from pharmaceutical dosage forms using near infrared microscopy*, Fiona Clarke, Vibrational Spectroscopy 2004 **34** 25–35

5.2.2. *Evaluating particle hardness of pharmaceutical solids using AFM nanoindentation* Victoria M. Masterson, Xiaoping Cao International Journal of Pharmaceutics 2008 **362** 163–171.

5.2.3. *Chemical imaging of pharmaceutical granules by Raman global illumination and near-infrared mapping platforms* Slobodan Sasic Analytica Chimica Acta 2008 **611** 73–79.

5.2.4. *Scalable Technology for the Extraction of Pharmaceutics (STEP): The transition from academic know how to industrial reality,* Ian Sutherland, Svetlana Ignatova, Peter Hewitson, Lee Janaway, Philip Wood, Neil Edwards, Guy Harris, Hacer Guzlek, David Keay, Keith Freebairn, David Johns, Nathalie Douillet, Chris Thickitt, Elsa Vilminot, Ben Mathews, Journal of Chromatography A, 2011 **1218** 6114– 6121.