Institution: University of Southampton

Unit of Assessment: 10 Mathematical Sciences

Title of case study: 10-05 Improved Drug Development Using Supersaturated Experiments

1. Summary of the impact

Collaboration between the University of Southampton and scientists at GlaxoSmithKline (GSK) has resulted in the adoption of new statistical design of experiments and modelling methods for the confirmation of a robust operating region for the industrial production of new drugs. These methods have enabled larger numbers of factors to be investigated simultaneously than previously possible, improving scientific understanding of the chemical processes and producing savings of time, money and effort. Southampton's new methods were used in a key process required for the registration of a new skin cancer drug with the US Food and Drug Administration, where the research enabled the verification of a robust operating region to be completed in a third of the previous time.

2. Underpinning research

Southampton has an established strong research programme in the development and implementation of methods for the statistical design and analysis of experiments that simultaneously vary a large number of factors. Such experiments are routinely used for *screening* (early stage experimentation to identify active factors having a substantial impact on a product or process) and, increasingly, for *robustness studies* (late stage experimentation to verify empirically derived models and system optimisation).

These experiments are regularly conducted by industry for the development of more efficient, economically viable products and processes, from drug development by pharmaceutical companies to performance improvements by car manufacturers. Successful screening and robustness studies both depend on *factor sparsity*, that is, when the performance of the system is dominated by a small subset of the factors; the quick identification of these few active factors can save considerable time and money.

From 2000 to 2006, research **[3.1]** by Professor Susan Lewis, Professor Angela Dean (at the Ohio State University; moved to Southampton in 2011) and PhD student Anna Vine (2001-2006) developed methodology for experimentation to investigate both individual factor effects and the joint effects of two factors. In particular, the research produced methods for exploiting information obtained from subject experts to provide a definition of a substantively important, or active, effect that can help to improve the effectiveness of data modelling from designed experiments. Assessments of the resulting design and modelling methods also incorporated realistic assumptions on the impact of inactive effects. This strand of research was funded by the EPSRC with project partners Jaguar Cars, Hosiden Besson and Goodrich, who were looking to solve complex engineering problems using Southampton's novel methodology.

Later research from 2007 onwards, by Professor David Woods, Lewis, Dean and PhD student Christopher Marley (2007 - 2011), focussed on supersaturated designs. It was supported by the EPSRC and industrial funding from both GSK and Lubrizol. These designs are used in experiments where there are fewer runs than factors in the experiment and are particularly useful when experiments are expensive to perform. This economy of resource makes supersaturated designs beneficial to industry but also presents challenges in the analysis of the resulting data. In fact, so controversial have these methods been that although they were first proposed in the 1960s, they have only very recently started to be applied in industry. Research at Southampton has played a significant role in this adoption through the provision by Marley and Woods **[3.2]** of (i) an assessment of the performance of supersaturated designs, and the associated data modelling methods, for different experimental scenarios, and (ii) the first recommendations for the

successful application of supersaturated designs.

Further research **[3.3]** developed new methods of selecting effective designs through minimising multi-factor dependencies, and optimal designs for robust product experiments. Most recently, the Southampton team provided the first evidence for the effectiveness of these novel methods for experiments with interacting factors and a new methodology for Bayesian modelling of data from supersaturated experiments **[3.4]**.

3. References to the research

Publications:

3.1 (*) Lewis, S.M. and Dean, A.M. (2001). Detection of interactions in experiments with large numbers of factors (with discussion). Journal of the Royal Statistical Society Series B, 63, 633-672.

3.2 Marley, C.J. and Woods, D.C. (2010). A comparison of design and model selection methods for supersaturated designs. Computational Statistics and Data Analysis, 54, 3158-3167.

3.3 Marley, C.J. (2011). Screening experiments using supersaturated designs with application to industry. PhD thesis, University of Southampton (supervised by D.C. Woods).

3.4 (*) Draguljic, D., Woods, D.C., Dean, A.M., Lewis, S.M. and Vine, A.E. (2013). Screening strategies in the presence of interactions. Accepted for Technometrics as a discussion paper.

(*) These references best indicate the quality of the underpinning research.

Grants:

3.G1 Lewis, S.M. (PI), Please, C.P. and Keane, A.J. Improved product design and manufacturing through economical experimentation. EPSRC, 2000-2003, £276,252.

3.G2 Woods, D.C. Supersaturated designs in pharmaceutical development. GlaxoSmithKline, 2010-2011, £5,000.

3.G3 Woods D.C. Efficient experimentation for effective identification of reliable design spaces, GlaxoSmithKline, 2012-2014, £195,189.

4. Details of the impact

The development of new medicines is a lengthy and costly procedure, with some estimates putting the average research and development spend as high as US$2 billion for each new drug **[5.C1]**. Speeding up this process not only saves on costs but frees up personnel to work on life-enhancing interventions elsewhere. Helping pharmaceutical companies find cost-effective ways of developing the chemical processes for new drugs has been a key driver of research into new statistical design and modelling methods carried out at Southampton. The resulting research has been pivotal in helping industry professionals fine tune their experiments at both the screening and robustness stages to maximise yield and minimise impurities.

Chemical development in the pharmaceutical industry is an inherently multi-factor problem, which requires the study of many chemical properties and process features. Hence, an important part of gaining understanding and knowledge of the system as economically as possible is the ability to investigate a large number of factors using only a small experiment.

Southampton's expertise in the design of experiments has led to a long-running relationship with GSK's Product Development team. As a direct result of the underpinning research, Southampton's supersaturated designs were successfully applied in a GSK-funded pilot project, which encouraged the GSK collaborators to adopt our methodology in the development of a number of new drugs. Since 2011 GSK has been performing approximately six experiments per year using Southampton's methodology, resulting in indicative savings of more than £25,000 and three weeks of scientists' time per experiment.

GSK scientists have applied Southampton's supersaturated experiments in the robustness step necessary to verify a drug's `robust operating region' - a US Food and Drug Administration (FDA) regulatory requirement for the registration of a new drug **[5.C2]**. A probabilistic, risk-based approach is taken to establishing this region through a sequence of experiments and associated statistical modelling. It is then verified through further experimentation, in which a large number of factors (input variables or process parameters) are varied to investigate whether or not they have a negligible impact on the response.

GSK drew on the research to verify the robust operating regions for two new drugs for metastatic melanoma, which were approved in 2013 by the FDA. Melanoma is the most serious form of skin cancer. The US National Cancer Institute has predicted that melanoma will cause more than 9000 deaths in the USA in 2013. Worldwide, there is a 50% one-year survival rate, with only 16% of patients in the USA surviving for five years **[5.1]**. For metastatic melanoma, the median age of a newly diagnosed patient is almost a decade younger than for other cancers.

The first application of Southampton's research was in the development of trametinib, a drug that inhibits a protein pathway involved in tumour growth which is activated in around 50% of melanoma cases **[5.1, 5.2]**. GSK's submission for FDA registration for trametinib included results from a supersaturated design developed by Southampton, which allowed the investigation of 16 factors in only 10 runs to verify a key stage in the development process. This design achieved a two-thirds saving in costs and time compared with GSK's previous standard approach of using a regular fractional factorial design, which would have required 32 runs to produce the data to ensure a quality product for the patient.

It is difficult to quantify the increased scientific understanding gained from the ability to perform experimentation involving a large number of factors that would otherwise be infeasible. This increased understanding is considered a key benefit of the new methods. *'The real importance to GSK of the successful application of these methods is the deeper scientific understanding gained through the ability to experiment simultaneously on larger numbers of variables than previously possible. This case study demonstrates the value of a long term relationship in enabling mutual understanding of scientific context and areas of opportunity.'* (John Whittaker, Vice President, Statistical Platforms and Technologies). Typically, a supersaturated design allows between a 1.5 and two-fold increase in the number of factors that scientists are able to investigate for a given resource. Thus, risk management can be significantly improved from the use of supersaturated designs.

To empower the scientists in GSK product development worldwide to use these methods, in 2011 the Southampton research team produced a protocol for finding and assessing suitable supersaturated designs using industry-leading statistical software (SAS JMP). They worked with SAS to produce a new piece of code to implement methods for best practice statistical modelling of the data obtained from using such designs. Southampton researchers advised on a tailored training programme that facilitated the use of these new methods in GSK's chemical development. *'Key to the successful use of the methods was the proactivity and engagement of UoS in translating high level research to application on GSK projects through collaborative work. This has provided case-studies to demonstrate value and enabled the development of training and mentoring approaches with key GSK staff'* (Martin Owen, Quality-by-Design Innovation Leader, GSK) **[5.3]**. GSK scientists have presented results from their application of supersaturated designs at a number of academic and industrial meetings, including at two Southampton-organised academic-industry events at the Isaac Newton Institute for the Mathematical Sciences in Cambridge.

As a measure of the value of the research to GSK, the pharmaceutical company awarded Southampton nearly £200,000 in 2012 to fund further fundamental statistical research from which future pharma benefits may be obtained **[3.G3]**.

5. Sources to corroborate the impact

Contextual References:

5.C1 Adams and Brantner (2006). Health Affairs, **25**, 420-428 (http://content.healthaffairs.org/content/25/2/420.long)

5.C2 'Guidance for Industry Q8 (R2) Pharmaceutical Development' US Department of Health and Human Services, Food and Drug Administration, Centre for Drug Evaluation and Research, Centre for Biologics Evaluation and Research. (http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073507.pdf)

Sources to corroborate Impact:

5.1 http://www.gsk.com/media/press-releases/2013/two-new-gsk-oral-oncology-treatments--braf-inhibitor-tafinlar---.html and references therein.

5.2 Ascierto et al. (2012). Journal of Translational Medicine, 10:85 (http://www.translational-medicine.com/content/10/1/85).

5.3 Senior Scientific Investigator and Quality-by-Design Innovation Leader, GlaxoSmithKline.