Institution: University of Leeds

Unit of Assessment: Chemistry (UoA 8)

Title of case study 2:
Knowledge-based genotoxicity prediction tools used universally in pharmaceutical development

1. Summary of the impact

Research at the University of Leeds has underpinned the company Lhasa Ltd. which has made widely available the toxicity prediction software currently known as Derek Nexus. The use of Derek Nexus by large pharmaceutical companies to support drug development is effectively universal. Toxicology prediction software has led to changes in guidelines issued by regulatory authorities and to industry-wide changes to the investigation of the toxicity of trace impurities. These changes have reduced the resources needed for experimental investigation of toxicity, and have increased revenues derived from launched drugs by extending their patent period of exclusivity. Lhasa Ltd. derives income in support of its charitable aims from Derek Nexus , and a related product Meteor Nexus (Meteor) also based on research undertaken in Leeds. The company reported revenues over £5.4M in 2012 and employs 71 highly qualified staff.

2. Underpinning research

A heritage of chemical informatics

A long-running collaboration involving the research group of **Johnson** at the University of Leeds and partners from the chemical and pharmaceutical industries led to the establishment in 1983 of Lhasa Ltd. (initially Lhasa UK Ltd.). This not-for-profit charity and company limited by guarantee, in which Johnson was a Director, was initially formed to develop tools, based on 'Logic and Heuristics Applied to Synthetic Analysis' (LHASA), that could automatically identify synthetic routes to complex organic molecules. Lhasa Ltd. secured subscriptions from a wide range of members from industry which was deployed by Johnson to fund academic research at the University of Leeds.

A member of Lhasa, Schering Agrochemicals, realised that adaptations to the LHASA approach could create a knowledge-based system to predict the toxic hazard of organic chemicals. An early prototype known as DEREK was developed in 1986 in collaboration between Lhasa UK Ltd. and Schering Agrochemicals. An account of the development of the Derek prototype has been published (Chapter 9 *in* "Knowledge-Based Expert Systems in Chemistry", P. Judson, RSC Theoretical and Computational Chemistry Series No. 1, RSC Publishing, Cambridge, 2009. ISBN: 978-0-85404-160-2).

Underpinning research to develop Derek Nexus into a mature system

Academic research undertaken by researchers at the University of Leeds between 1993 and 2005 enabled DEREK (subsequently Derek for Windows and now, Derek Nexus) to be developed into a mature system that is accepted industry-wide.

A key study was undertaken by **Long** in collaboration with FRAME (Fund for the Replacement of Animals in Medical Experiments) to evaluate the viability of Derek's approach for toxicity prediction. Tested with a panel of food-based carcinogens and mutagens, the potential of the system was demonstrated, whilst also highlighting the need to enhance reliability through exploitation of larger experimental datasets (1). This study highlighted the accuracy and reliability of Derek for industry and drove a new phase of the model's refinement.

Research undertaken between 1993 and 1996 led to a refined model with improved predictive capabilities, particularly in the areas of genotoxicity and skin sensitisation (2). This highly-cited work was undertaken principally by **Marchant**, with **Langowski** and **Judson**, and involved collaboration with industrial partners. The refinement of rules improved substantially the ability of Derek to predict the toxicity of compounds (3).

In addition, through expert software engineering, the interface and data processing capabilities of the Derek tools were enhanced with a simple graphical interface for the input of structures and display of results. Leeds researcher **Patel** also led the development of a graphical language (StAR) for the representation of generic structures within the Derek platform (4).

Underpinning research to extend to metabolism prediction

Alongside the continued research to improve Derek, Leeds researchers **Vessey**, **Long**, **Button**, **Greene** and **Judson** developed and applied knowledge-based prediction techniques to create a complementary system called METEOR (currently Meteor Nexus). Meteor uses a similar rule-based approach to predict the metabolic fate of compounds. Meteor provides a further level of sophistication to toxicity prediction by identifying potential sites and routes of metabolism (5,6).

The underpinning research was published in leading cheminformatic and toxicology journals and the six cited references have collectively amassed well over 250 citations (1-6).

Key personnel

Peter Johnson, Lecturer, 1980-4 then Senior Lecturer, 1984-95 then Professor, 1995-2004 then Research Professor, 2004-.
Anthony Long, Project Officer, 1990-2005.
Jonathan Vessey, Project Officer, 1995-2005.
William Button, Computer Scientist, 1999-2002.
Nigel Greene, Software Assistant, 1998-1999.
Mukesh Patel, Project Assistant, 1995-2005.
Carol Marchant, Project Officer, 1993-2005.
Jan Langowski, Senior Project Officer, 1986-2005.
Philip Judson, Research Fellow then Manager, 1991-1998.

3. References to the research

1. Long, A. and Combes, R.D. (1995). Using Derek to Predict the Activity of Some Carcinogens and Mutagens Found in Foods. *Toxicology in vitro,* 1995, 9, 563-569. (10 citations; Source: Source: Scopus, 24/10/13) http://dx.doi.org/10.1016/0887-2333(95)00040-F
2. Ridings, J.E., Barratt, M.D., Cary, R., Earnshaw, C.G., Eggington, C.E., Ellis, M.K., Judson, P.N., Langowski, J.J., Marchant, C.A., Payne, M.P., Watson, W.P. and Yih, T.D. (1996). Computer Prediction of Possible Toxic Action From Chemical Structure - an Update on the Derek System. *Toxicology,* 1996, 106, 267-279. (110 citations; Source: Scopus, 24/10/2013) http://dx.doi.org/10.1016/0300-483X(95)03190-Q
3. Greene N; Judson PN; Langowski JJ; et al. Knowledge-based expert systems for toxicity and metabolism prediction: Derek, StAR and Meteor (1999) *SAR and QSAR in Environmental Research* Vol. 10 2-3 pp 299 (107 citations; Source: Scopus, 24/10/2013) http://dx.doi.org/10.1080/10629369908039182
4. Tonnelier, C.A.G., Fox, J., Judson, P.N., Krause, P.J., Pappas, N. and Patel, M. (1997). Representation of Chemical Structures in Knowledge-based Systems: The StAR System. *Journal of Chemical Information and Computer Sciences,* 1997, 37, 117-123. (11 citations; Source: Scopus, 24/10/2013) http://dx.doi.org/10.1021/ci960094p
5. Button, W. G.; Judson, P. N.; Long, A.; Vessey, J. D. (2003). Using Absolute and Relative Reasoning in the Prediction of the Potential Metabolism of Xenobiotics. *Journal of Chemical Information and Computer Science,* 2003, Vol. 43, No. 5, pp. 1371-1377. (39 citations; Source: Scopus, 24/10/2013) http://dx.doi.org/10.1021/ci0202739
6. Balmat, A-L.; Judson, P.; Long, A. and Testa, B. Predicting Drug Metabolism - An Evaluation of the Expert System Meteor. *Chemical and Biodiversity.* 2005, Vol. 2, No. 7, pp. 872-885 (42 citations; Source: Scopus 24/10/13) http://dx.doi.org/10.1002/cbdv.200590064.

All papers are in internationally-leading peer-reviewed journals and are hence ≥2*, but references 2, 3 and 5 are particularly highlighted to demonstrate the quality of the underpinning research.

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

The ability to predict potential significant toxicity of pharmaceutical impurities is of vital importance to the pharmaceutical industry because many drug candidates fail in development due to toxicity

problems. Early toxicity testing can prevent the costs associated with unnecessary R&D and the late failure of drug candidates.

Universally accepted by regulators

In 2008 the US Food and Drug Administration (FDA) published guidance on *"a variety of ways to characterize and reduce the potential lifetime cancer risk associated with patient exposure to genotoxic and carcinogenic impurities both during clinical development and after approval."* Derek Nexus is specifically cited as a recommended prediction tool to inform decision-making (A). Although a number of methods are mentioned alongside Derek Nexus for this initial toxicity evaluation, in practice, the use of Derek Nexus by large pharmaceutical companies is effectively universal (B). In a survey of eight leading pharmaceutical companies in 2012, Derek Nexus was the method of choice for all eight companies in assessing genotoxic risk; in half of cases, Derek Nexus was the only commercial product used (C). An article from 2013 co-authored by representatives from 15 companies confirms the on-going value of Derek Nexus in the drug development process (D). **Changes to guidelines have been informed** and the **pharmaceutical sector has adopted** Derek Nexus as a tool for toxicology prediction.

Faster to market to increase revenues

The universal application (C,D) of the Derek Nexus system between 2008 and 2013 derives from its excellent success rate in identifying structures that represent a genotoxicity risk and providing supporting evidence for its assertions (C,D). The success of Derek Nexus has embedded the software in the workflow **industry-wide** as a means of reducing costly and time consuming experimental evaluation. An article co-authored by representatives from 13 major pharmaceutical companies explains how Derek Nexus can accelerate the development process, whilst still ensuring the regulatory requirements to ensure patient safety are met; the article places the success of *in silico* approaches (judged using the industry-accepted negative prediction value) at 94%, which increases to 99% with interpretation by an expert user (*Regulatory Toxicology and Pharmacology*, 2006, **44**, 198-211).

One pharmaceutical company shared some experiences of two development programmes that led to launched products over a 5-year period before the industry-wide acceptance of toxicology prediction tools. In each programme, the regulatory authorities raised concerns about the genotoxicity profile of a low level impurity, leading to a 1-3 month delay while the safety of the impurity was established experimentally. In each case, a Derek Nexus-based assessment would have been negative, and would have avoided any delay. As it was, based on a conservative estimate of the delay (1 month) and a conservative estimate of the annual sales figure for the launched products during their patent period of exclusivity (each £200M), the use of Derek Nexus, now embedded in current practice, would have increased revenues by £30M. If this scenario is common to all large pharmaceutical companies, then the increased revenues across the sector over a 5-year period (using a conservative scaling factor of five-fold) can be estimated at £150M. The Director of Computational Toxicology at GlaxoSmithKline corroborated in 2012 that the impact of embedding prediction tools (in particular Derek Nexus) for genotoxicity in current practice was broadly in line with his experience and a realistic assessment for the sector as a whole (E). **The performance of a sector was thus improved**.

Reduced costs during development

The embedding of predictive toxicity tools has also had a **significant bearing on cost and resource**. Each year, on average, a major pharmaceutical company might perform 100 Derek Nexus screens on impurities to adhere to regulatory guidelines for genotoxic impurities. Of these, a significant proportion (>50%) will generate a clean signal and, as a result, development can proceed without further safety testing. In the absence of a reliable predictive tool embedded in industry practice, experimental screening would require substantial resource for synthesis, purification, analysis and testing. Assuming an FTE rate of £100K, and applying a conservative resource requirement of 0.25 FTE-year, a cost saving of £25K per example can be estimated. Scaling for 50 clean signals per year, and applying a conservative scaling factor for the industry of 5-fold, this corresponds to an estimated cost saving of £30M over a five year period. The Director of Computational Toxicology at GlaxoSmithKline corroborated in 2012 that the impact of embedding toxicology prediction tools (in particular Derek Nexus) in current practice was broadly in

line with his experience and a realistic assessment for the sector as a whole (E).

Employment and revenue

Lhasa Ltd. is a not-for-profit company (and a registered charity) and is responsible for the continued support of cheminformatic research undertaken at the University of Leeds in support of its charitable aims. There are currently 254 organisations who are members of Lhasa Ltd., including all of the top 20 pharmaceutical companies in the world (F).

In 2005, the research capacity supporting Lhasa Ltd's development had grown substantially, and the staff left the employment of the University and became employees of Lhasa Ltd. Lhasa Ltd.'s growth has accelerated dramatically in the last five years (see Table below) (G,H). In 2012, Lhasa Ltd. reported an annual turnover of >£5.4M; the Derek Nexus system contributed 56% of turnover, with Meteor Nexus (18%) and other more recent products based on Leeds research providing further major contributions (G). In 2012, Lhasa Ltd. employed 71 highly qualified staff (G). **The company has therefore established its viability and generated revenue.**

Table of income and staff numbers at Lhasa Ltd., 2007-2012

Year	Income (£000s)	Staff
2007	3,028[a]	51
2008	3,819[a]	58
2009	4,379[a]	59
2010	4,442[a]	61
2011	5,063[a]	69
2012	5,416[b]	71

[a]Audited accounts. [b]Management accounts.

The introduction of Meteor Nexus alongside Derek Nexus adds a layer of sophistication which addresses a key gap in toxicity prediction: the ability to predict potential metabolic routes, together with the prediction of the toxicity of the predicted metabolites. Lhasa Ltd.'s strategy for continued growth focuses on Meteor Nexus as a key product alongside further development of Derek Nexus to meet the needs of end-users in the pharmaceutical industry.

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

A. "Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches", U.S. Department of Health and Human Services, Food and Drug Administration, 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079235.pdf
B. "New Horizons in Predictive Toxicology: Current Status and Application", ed. Alan G.E. Wilson, RSC Drug Discovery Series No. 12., RSC Publishing, Cambridge, 2012. ISBN: 978-1-84973-051-8 (Section 5, reference 5, page 91).
C. "In silico methods combined with expert knowledge rule out mutagenic potential of pharmaceutical impurities: An industry survey", Regulatory Toxicology and Pharmacology, 2012, 62, 449-455. http://dx.doi.org/10.1016/j.yrtph.2012.01.007.
D. "Use of *in silico* systems and expert knowledge for structure-based assessment of potentially mutagenic impurities", *Regulatory Toxicology and Pharmacology* 2013, **67**, 39-52. http://dx.doi.org/10.1016/j.yrtph.2013.05.001
E. Statement, Director of Computational Toxicology, GlaxoSmithKline, 11th December 2012.
F. List of current members of the Lhasa Ltd.: http://www.lhasalimited.org/membership/current-members.htm (accessed 11.9.2013).
G. Statement, CEO, Lhasa Ltd, 5th February 2013.
H. Lhasa Ltd accounts, dated December 2012.