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MEETING REPORT

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Addressing the Innovation Gap

by Phillip Jeffrey, Peter Warne and Robert Williams

Summary

The 10 years since the mid-1990s have witnessed an unprecedented investment in Drug Discovery driven by both the unraveling of the human genome and the parallel introduction of various high-throughput technologies. During the same period, industry metrics describe a decline in the numbers of new molecular entities launched upon the global pharmaceutical markets. The Society for Medicines Research (SMR) meeting entitled "Addressing the Innovation Gap" brought together a program of expert speakers to comment upon the challenges currently facing the pharmaceutical industry and some of the measures being undertaken to enable future success.

The Innovation Gap in the pursuit of new pharmaceutical agents was predicted in the mid-1990s and based on the then, falling numbers of new drug approvals. New drug discovery technologies in both chemistry and biology were widely introduced at an investment rate second only to the costs of clinical research. New drug approvals remain lower than in the 1980s and early 1990s, and seven distinguished speakers were assembled at the March meeting of the Society for Medicines Research (SMR) to suggest reasons why and some means for reversing the trend.

Dr. Simon Campbell was Worldwide Head of Pfizer Drug Discovery during its most productive era. He was a key member of the research teams which discovered *Cardura*® (**doxazosin**) and *Norvasc*® (**amlodipine**) (leading products in each of their therapeutic areas) and was senior author on the paper that led to the development of *Viagra*® (**sildenafil**). His analysis shows that predictions for pharmaceutical growth over the last 10 years have not been fulfilled. With hindsight, 10% future growth year on year appears to be an over optimistic estimation. The figure may be closer to 5% annually which, in numerical terms, equates to a loss of about USD 150 billion over the next few years. And the future holds further threats particularly in the world's largest pharmaceutical market, the United States.

Each year, the United States spends over USD 250 billion on medication in an atmosphere of unregulated national drug prices. Both patients and payers are starting to rebel against these costs and importation from both Canada and Mexico is rife. Furthermore, a Democratic government is expected to intervene in an effort to curb expenditure. With the U.S. market accounting for 45% of the total world spend (and 70% of profits), the profit trend would appear to be downwards.

The European markets are no more sympathetic. The use of either *Aricept*® (**donepezil**; Alzheimer's disease) or leupeptin (muscular dystrophy) is not to be reimbursed by the U.K. authorities. Scotland is not convinced by the economic arguments for use of *Sutent*® (**sunitinib malate**; anticancer) and Germany does not regard obesity as a disease so that drugs to treat the disorder will not be financed. Investment in R&D is dependent upon current profits so that if these are eroded, investment too will diminish.

The costs of drug development continue to rise and have now passed the USD 1 billion per product mark. In tandem, the numbers of approvals have decreased from more than 50 in 1996 to 18 in 2005. Further analysis, however, shows that the number of new mechanistic entities (including a move towards biologicals in addition

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to traditional small molecules) has remained relatively constant; it is the numbers of products with small incremental gains which have proved more difficult to register. In short, new drugs have to be significantly better if they are to be approved.

Consequently, the industry has witnessed many changes of senior management, cost saving programs and job losses, and share prices, in this once popular investment area, have been dropping since 2001. All this can be traced to mistakes made by the industry; an overreaction to the threat of cost control by the Clinton government (which ultimately was not approved), a biotechnology explosion which is not yet returning the investment and exaggerated market expectations. More worrying, these commercial influences are making science a less attractive option for study and the overall science base is weakening.

A slavish commitment to the messages derived from industry metrics has promoted the installation of high-throughput systems but it may yet be too early to judge the success of the technology. However, it is apparent that product attrition remains in the 1:10 region and while the numbers of phase I and phase II candidates are increasing, phase III numbers are not! The reasons for the losses have been skewed away from pharmacokinetics (a major cause prior to the introduction of high-throughput ADME screening) which must be regarded as a success. Currently, some 20% of development candidates are still lost for commercial reasons (unable to compete) and toxicity levels have risen to 15%, but the major cause of failure is a lack of efficacy (or sufficient efficacy).

The current response of the industry is to cultivate collaborative programs with academia (see Colin Wyatt in this report) and move back towards small-molecule research rather than biologicals (although antibody technology remains very important). And these two sectors are starting to converge (see Alastair Lawson in this report). Investment is broadening; most notably in China particularly in generic products. Academic links are too, being forged throughout the world but expect this to be longer term. It is more difficult, subject to cultural challenges and, the economists predict, salary differentials will erode rapidly.

In conclusion, drug discovery remains an extremely challenging area. There are new technologies which have taken time to learn and optimize and there is no shortage of drug targets. Approximately 320 pathological target types have been exploited to date. The human genome contains approximately 30k genes producing many more gene products. The challenge remains the identification of relevant targets and susceptible patient populations.

Dr. Campbell's industry overview was followed by a presentation from Dr. Roger Hickling, Director of R&D at Alizyme. The company was established in 1995 and currently has four products in phase II/III development. Alizyme employs a virtual approach to drug discovery and development, possessing a core of just 20 employees. Operationally, the company outsources all experimental work and works with an extensive network of scientific, regulatory and medical consultants. This approach allows Alizyme to retain strategic control of its programs while allowing maximal spend on direct project activities and minimal spend on infrastructure. Alizyme's products are sourced from support of external drug discovery or inlicensing from academic groups or companies, including "fall out" from mergers and acquisitions. Dr. Hickling indicated that relatively small virtual companies need to focus very tightly on managing commercial risk. Alizyme uses formalized analytical tools to understand as clearly as possible likely financial returns. In terms of drug development, Alizyme does not manage projects by addressing in a temporal manner regulatory requirements for preclinical and phase I/II/III studies. Rather, Alizyme project managers focus on identifying areas of greatest drug development uncertainty and plan activities to address key risk areas up front.

Dr. Hickling agreed with Dr. Campbell's comments on the importance of selecting the right therapeutic targets for drug development and the need to focus on choosing the most appropriate patient populations. However, Dr. Hickling pointed out that there is opportunity for innovation in product development and that innovation was not restricted to identifying "first-in-class" molecules. As an example, he referred to Alizyme's *Colal-Pred*® program for the treatment of ulcerative colitis. **Prednisolone** is an effective treatment for this disease but its use is limited by systemic side effects. The Colal-Pred program delivers prednisolone using a proprietary colonic delivery device which maximizes local steroid delivery to the disease site with minimal systemic exposure. Dr. Hickling also described the development program for **cetilistat**, a potential treatment for metabolic syndrome. Cetilistat is a lipase inhibitor that was identified through a structure-based design program sponsored by Alizyme. **Orlistat**, the first in class lipase inhibitor is associated with problems of inducing oily stools. In phase II trials in obese diabetic patients, cetilistat and orlistat produced similar reductions in weight loss and blood HbA1c levels. However, fewer discontinuations were observed due to gastrointestinal-related adverse events with cetilistat. This result may be due to differences in physiochemical properties of the two drugs, and Dr. Hickling pointed out that this was another example of innovation other than the finding a first-in-class compound.

A comparison of small-molecule and antibody-mediated therapies shows that the latter, all too often, are more expensive to develop, more difficult to administer and their potential benefits limited by unsuitable pharmacokinetics. However, the manner in which an antibody binds to its target can aid the discovery of small molecules and this is the basis of the

A2Hit™ technology described by Dr. Alastair Lawson. Using this approach, together with UCB SLAM (Selected Lymphocyte Antibody Method) technology, his team are seeking the *in vivo* validation of drug targets, investigation of potential therapeutic axes and identification of the coordinates of the sought after epitope.

The biology of interleukin-6 (IL-6) was used as an example. The activity of this cytokine is complex and there are several points for potential interaction: IL-6 receptor binding, recruitment signaling and hexamer formation, for example. The application of UCB SLAM technology enables multiple antibody formation from each of these potential sites and subsequent enrichment through the isolation and cloning of individual B lymphocytes. With this technology is derived a highly specific antibody without the need for a fusion event or subsequent engineering.

In this way, UCB SLAM has generated two reagents: one which blocks the interaction of IL-6 with its receptor and another which blocks IL-6–mediated signal recruitment. With these two antibodies, there is a clear separation of responses to IL-6 and advantages for either approach have been demonstrated for the modulation of IL-6 activity.

The technology has multiple applications. New sites (epitopes) can be probed for biological impact through generation of specific antibodies, and unlike classical receptorology, there is no limitation to the site of ligand binding. UCB SLAM identifies all potential sites of interaction be they allosteric, previously unknown sites or new epitopes at known sites. Furthermore, target identification is not limited to the dimensions which restrict small molecule probes (currently estimated to be in the region of 1–10% of the genome. Antibody technology enables exploration of all 30k gene products. And it turns out that analysis of the data is suitable for its own brand of bioinformatics. There is a high sequence convergence in active, function-modifying antibodies against a given target at a given site, which enables the classification of antibody families. The next steps are to tie these analyses with the generation of small-molecule libraries and provide another viable alternative to random screening.

The current atmosphere of increasing costs with diminishing returns is not the only criticism of the pharmaceutical industry. It is also accused of failing to generate innovative advances, paying too little attention to world healthcare needs and lacking the required breadth of expertise. Small wonder that it is turning (or returning) to collaboration with academia. Such interactions and agreements were widespread in the 1940s but declined during the bumper years of the 1960s to 1980s. Since then, however, the wisdom of working with university and small company departments has increased. The arrangement has mutual benefits; the industrial partner gains access to specialist expertise established over many years. The academic group receives essential funding, of course, but it also gains the means of exploiting its inventions and is made aware of commercial issues to which it would not otherwise be exposed.

The stage would seem to be set for prosperity on both sides but, while many collaborations are successful, many more are not. The reasons can be as simple as misalignment of objectives, a failure to clarify the expectations of each group at the outset. Although less marked than once they were, there remain cultural differences which frequently result in a failure to meet project goals, particularly in terms of timelines. Academic units do not easily adopt a subservient role which may be essential for the provision of optimized pharmaceutical leads. Conversely, there is often a failure on the part of industry to recognize and use academic resources in the most appropriate manner.

The above observations were made by Dr. Colin Wyatt in his presentation "Bridging the Innovation Gap between Academia and Industry" referring to the failure of many academic groups to qualify their inventions in terms of target validation and, in turn, preparing them for scrutiny by potential partners. Thus, the innovation gap in academia runs from target validation through to phase I clinical trials.

There are several components to this shortcoming. Although the capabilities are usually satisfactory (or better), there is a limited capacity to meet industry standards. Equally, academics are unwilling to adopt a service function which can seriously hamper optimization processes. And management practices are often at a lower level (or priority) so that projects may not be appropriately coordinated, project managed or made commercially attractive.

Several models are being examined by various groups, most notably MRC technology, Cancer Research Technology (CRT) and its partner Cancer Research UK (CR-UK). At Imperial College in London, the university is harnessing its drug discovery capability under the label of "Imperial Innovations" to generate a self-sustaining and suitably scaleable organization which will interact with industry on a professional footing. The business model is a competency led strategy designed to leverage interdisciplinary research. Much of the expertise already exists (or can be readily accessed) but it is currently disjointed. The management team is now in place to integrate these areas and develop an increased level of understanding so that academics can be motivated to follow and develop their ideas.

Addressing the thought-provoking topic of "Data Driven Drug Discovery—Fact or Fiction", Dr. Darren Green (Director of Informatics, GlaxoSmithKline [GSK], U.K.) reviewed the increasing investment that the pharmaceutical industry continues

to make in informatics technology. However, despite the advances during the last 10 years in automated synthesis, screening protein expression and, –omics sciences in general, clinical evidence supporting the hypothesis that scaling up existing experimental processes will lead to an increased production of drugs to market is still lacking. While increasing automation has led to an increase in the amount of data produced, the evolution of decision-making processes required to keep pace has not been forthcoming. As a direct consequence, Dr. Green observed, the industry must change its ways and stop making compounds that continue to fail, focus more on the decision-making processes and use the science of informatics in a proactive rather than reactive manner.

Informatics is a combination of computer science, computational science and statistics. It can, and should be, applied across the whole drug discovery and development paradigm and reflects the fact that, like the world we live in, drug discovery is multidimensional. Decisions are made based on more than one parameter and these can be ranked in terms of their relative importance which may vary depending on current trends, personal preference, etc. Such an informatics-based approach has been applied at GSK where the screening collection has been strategically managed and balanced with respect to three key parameters: 1) success in screening the compounds; 2) chemical tractability and 3) developability or drug-like properties of the molecules. The GSK collection model evaluates the compounds that are required to be synthesized in relation to the compounds that are already available, in order to maximize the success of the collection of the whole. Using a mathematical model that defines the relationship between chemical diversity and success in lead generation, Dr. Green and his coworkers have been able to define the value of new compounds considered in the context of the existing collection.[1]

Dr. Green described in detail the use of this approach and how it should always be used in an integrated manner, analyzing several parameters simultaneously rather than just one simple cut-off value from a single IC_{50}. In looking to the future, Dr. Green highlighted the progress that has been made in high-throughput screening analysis, library design and predictive modeling, but reflected on the need for more investment in informatics skills and decision support infrastructure. This will help bridge the gap between the "wet" and the "dry" sciences (i.e., the data generation and data analysis) which must be resolved in order to maximize the investment in current technology.[1]

In reviewing advances in drug development from a clinical perspective, Dr. Steve Toon (Executive Director, SimCyp Ltd, U.K.) highlighted opportunities for a thorough reappraisal of the current process—"Joined Up Thinking Along the Critical Path". Contrary to popular belief, clinical drug development is not the seamless continuum it aspires to be. Despite much progress in recent years, there are still too many internal barriers and hurdles to a seamless and integrated approach to clinical development and this situation has prompted the Critical-Path Initiative which has been initiated by the Food and Drug Administration (FDA) of the United States. Traditionally, early phase I studies have provided the opportunity to test new drugs in healthy volunteers at relatively low cost. Historically, these studies have been designed to provide only limited information on human tolerability and pharmacokinetics although these are no longer the reasons why drugs fail. While in the 1980s it was recognized that approximately 40% of drugs failed in phase I due to "poor" pharmacokinetics, our ability to predict human pharmacokinetics through advances in the enzymology of drug metabolism, molecular structure/activity relationships and *in silico* and *in vitro* modeling techniques have now reduced this figure down to approximately 10%. However, our ability to predict biological response is neither as advanced nor as sophisticated and Dr. Toon called into question, whether or not the use of healthy human volunteers to quantify and predict the therapeutic potential of new drug candidates is appropriate.

In comparing and contrasting the case for using patients or volunteers, Dr. Toon highlighted that, while the fundamental assumption that the pharmacokinetic profile in healthy volunteers is often (though not always) regarded as the same as in the patient population, biological response is not. However, judicious use of biomarkers and therapeutic models (e.g., the Public Speaking Model for assessing novel anxiolytics and the Cold Pain Model for assessing novel analgesics) can provide pivotal decision-making data from early clinical studies in healthy volunteers. This move in early clinical development from simple human toxicology towards an integrated, investigative, quantitative approach to experimental medicine was making good progress, up until the recent events with the **TGN-1412** trial.

Now more than ever, Dr. Toon advocated, phase I study protocols must be developed on a case-by-case basis and not simply prescribed by regulators. Early clinical development study populations should be chosen based upon drug safety and scientific relevance to evaluate patient susceptibility to both disease and drug. Drawing on parallels with the "3R's" (reduction, refinement and replacement) every clinical study should add to the knowledge base, maximize the amount of scientific information gathered, measure a biological response wherever possible and, if necessary, replace the human volunteer with the patient. From simple pharmacokinetic/pharmacodynamic modeling to sophisticated models of disease progression, clinical trial design and simulation, modeling and simulation tools will have an increasing role to play in

providing the framework for this paradigm of joined-up thinking.

Metabonomics is the quantitative measurement of time-related mutiparametric metabolic responses of living systems to pathophysiological stimuli or gene modification. In presenting "Metabonomics Technologies and their Applications in Pharmaceutical Discovery and Development", Prof. John Lindon (Dept. of Biomolecular Medicine, Imperial College, London, U.K.) emphasized that metabonomics bridges the gap between transcriptomics and proteomics and by use of appropriate endpoint markers provides evidence for disease diagnosis and evaluation of beneficial or adverse drug effects. Metabonomics is a systems-based approach studying the small-molecule metabolites of a biology system and is usually conducted on biofluids (e.g., blood and urine). Core analytical technologies are those based around providing molecular structural information and include mass spectroscopy and nuclear magnetic resonance spectroscopy. Such techniques detect changes in the metabolic response of an organism to a particular disease, toxin or pharmaceutical compound.

However, in order to understand the interrelationships between the various data sets, extended statistical and mathematical concepts are required for the integrated analysis of these multifactorial phenomena. Normalization and transformation processes are of great importance, as is the detection of significant correlations between the different components. Analytical techniques such as clustering, PCA (principle component analysis) and STOCSY (statistical total correlation spectroscopy) were introduced. Using such techniques, Prof. Lindon demonstrated the power of metabonomics in understanding and predicting hydrazine toxicity in rats. Data and interpretation from the 3-year COMET study (Consortium on Metabonomics in Toxicology), where some 147 toxicants were evaluated in the rat by five pharmaceutical companies, have identified several predictive screening methodologies and novel biomarkers for predicting a toxicological outcome. Population Metabonomics studies in humans (INTERMAP and INTERSALT studies) have been successful in distinguishing people metabolically by age, gender, body mass index, smoking habits and diet and even those at risk from type 2 diabetes and apoE3-mediated atherosclerosis.

Prof. Lindon concluded that while metabonomics is already playing a role in improved, differential diagnosis and prognosis of human diseases, the emerging discipline of "Pharmacometabonomics" will be the next logical step. Based on the analysis of an individual's predose metabolic profile, the metabolism, efficacy and toxicity of new drug entities will be predicted. Perhaps the first steps to personalized medicines have indeed, already been taken.

References

1. Harper, G., Pickett, S.D., Green, D.V. *Design of a compound screening collection for use in high throughput screening*. Comb Chem High Throughput Screen 2004, 7(1): 63–70.

Peter Warne (Biointerface, U.K.), F. Phillip Jeffrey (GlaxoSmithKline, U.K.) and Robert J. Williams (Cancer Research U.K.) are members of the Society for Medicines Research (SMR) Committee, which organizes conferences on behalf of the SMR. Details of forthcoming meetings can be obtained from the SMR Secretariat: 840 Melton Road, Thurmaston, Leicester, LE4 8BN, U.K. Tel: +44 (0)116 269 1048; Fax: +44 (0)116 264 0141; E-mail: secretariat@smr.org.uk; URL: http://www.smr.org.uk.