Chromatography Today talks to Howard Hill

by John Lough

Up until now, interviewees featuring in Chromatography Today have been drawn from individuals who have been recipients of Martin or Jubilee Awards of The Chromatographic Society. Illustrious though this group very much is, they do not have exclusive ownership of all comment that is worth making in the field of analysis and separation science. Accordingly, we are more than happy to turn to Howard Hill (of contract researchers HLS) who not only has his finger on the pulse regarding biopharmaceuticals and their analysis but is also the lead of the team charged with nurturing the legacy of the late Eric Reid that is the Reid International Bioanalytical Forum. Howard's main responsibility is orchestrating the high quality scientific programmes that characterize the Reid meetings; so he knows what he is talking about. Here Howard talks to Chromatography Today not only about biopharmaceuticals but also about what is in store for us in this year's Reid meeting in early July.

(Chromatography Today) Several years ago you noted the increasing proportion of biopharmaceuticals in pharmaceutical company pipelines. What were the drivers and just how far have things gone now?

(HH) In some cases biologics are able to target receptors that are not amenable to small chemical entities; there was and probably still is a school of thought that better designed small molecule mimetics could be identified to target any ligand. However the success of some of the early biologics, mostly recombinant forms of endogenous proteins and other important classes such as monoclonal antibodies have proven to be extremely successful in treating life threatening conditions. These "large" molecules now represent up to 50% of many companies' development portfolios. Indeed there is common agreement amongst most industry observers that by 2014 the top six block busters will be biologics.

What are the drivers causing the current changes in the Pharma Industry.

There are really a variety of changes, a major one being the move to biologicals as described above; another is reduction in new therapeutics registered year on year for the last ten years. This coupled with the patent cliff i.e. where most blockbusters will become generics in the next few years, initiated a round of mergers which in some cases were designed to buy in existing blockbuster molecule sales while diversifying the merged entities portfolio. However this did not result in an increase in new molecules so together the failure of research and loss of revenues has resulted in the need to cut costs, the most prominent recent casualty being Pfizer in Sandwich. There is an increasing trend to off shoring the early discovery, while maintaining the IP around targets and molecular design, and/or joint ventures with academia and spin out discovery companies. There is a nice article in the RSC journal which, if not a correct interpretation of current and future events, is one with which I certainly agree

This February, your company staged a "Biologics" symposium at Cambridge. How did things go?

The Biologics symposium in Cambridge sponsored by HLS, was a great success, the auditorium was full and the mix of presentations excited a lot of discussion.

There were over 160 registrants. While this is the first in a series of such symposia, HLS organized a similar meeting at Clare College on Advanced Therapies last year. This year was a wider ranging meeting and attracted a much larger audience and had to be moved to the larger auditorium.

The diversity of monoclonal antibodies was illustrated be Dr Mike Clarke (Cambridge University) who illustrated that even within this single therapeutic class there are many technological variations. This started with the production of monoclonal antibodies around 1980 using hybridoma technology. Monoclonal antibodies now range from genetically engineered chimeric antibodies through humanized and full human antibodies generated using a wide range of approaches including mouse immunization, phage display and human monoclonals produced in mice. In addition, receptor polymorphisms are likely to result in the production of subsets of monoclonal therapies able to meet these needs; variations on a theme seem infinite.

While biological therapies have been around a long time, their diversity and rapid growth has meant that industry is learning and evolving its approach so the development process which is truly on a case by case basis – something that was may have been lost in the small molecule field which used to be developed in a standard format. The current approach for biologics is more fit for purpose; this means that the industry, pharma companies, CROs are all learning and regulators need to share their understanding and take a proactive science driven and less prescriptive approach to drug development.

At HPLC 2010 in Boston and elsewhere there has been discussion of "top down" and "bottom up" approaches to the analysis of biopharmaceuticals. Are both approaches needed? Is LC-MS already eclipsing immunoassay?

I guess this means how concerned are we about small variations in the actual structure of the molecule compared with methods such as immunoassay that measure only one component of the molecule i.e. the binding epitope. Can you relate small changes in structure to changes in activity-do you need to!?

LC-MS is a long way from eclipsing immunoassay; throughput and sensitivity are the two main pros for immunoassay while LC-MS strictly speaking can be set up relatively quickly and for small proteins / peptides is probably the method of choice for this group of compounds.

If we get to the stage where we can measure routinely 10-20 variants of a molecule all with similar biological activity then we may be over specifying the requirements. However understanding the correlation of structural based assays with other assay types is important to know. At the last Reid Forum we had a session organized by John Smeraglia on essentially this topic where Ezan showed a difference in plasma levels between the LC-MS approach and a ligand based approach. In fact Eric Ezan goes into great detail on this in a recent special edition of Bioanalysis.

Is there a strong regulatory influence on how biologics must be analysed?

as the PK discussion group and more latterly with the Bioanalytical Zone website launched mid March 2011, there is nothing like getting people together to be open and frank about their problems.

Do you find that company bioanalysts are still prepared to openly discuss the problems they are facing and compare notes with bioanalysts from competitor companies?

As discussed above, this does take place more on an informal basis while the number of formal problem-exposing talks has diminished. However, it may be that because of the diversity and the need to cover so many areas, less emphasis on discussing common problems is inevitable.

Do you expect that cuts in Drug Discovery in the UK will strongly affect the total amount of drug bioanalysis being carried out here or will it simply mean that different people are carrying out the bioanalysis?

Whoever carries out bioanalysis means there will be a demand for information exchange. The demise of the number of major innovators from about 30 companies in the seventies to a handful now does not mean there will be fewer drugs or less bioanalysis taking place. Pharma (currently) is moving to the virtual model while many smaller companies are being spawned as big Pharma downsizes and in some cases universities are developing capabilities in this area. So yes the number of Bioanalysts will not decline but come from a broader range of backgrounds and interests. I believe the audiences are now more eclectic than ever, be it on age, status and analytical expertise.

The major threat to any scientific meeting is if target audience dwindles because drug development in its entirety is off shored and the West becomes an owner of the IP only i.e. target id and design of the drug molecule and a marketing / sales operation – many companies are trending towards this model, some overtly others more subtly.

I hope the Pharma industry in the West does not go the way the manufacturing industry has gone – but that is another discussion.

The Forum is a great opportunity to cross fertilize ideas – share experiences and above all to develop knowledge in a wide range of developing technologies to measure an even wider range of therapeutic molecules.

Perhaps one of the most engaging talks was that presented by Robin Thorpe (NIBSC) who engaged the audience for over an hour on the Tegenero story. While not a classical PK story it certainly threw more light on the understanding of the mechanism of action of these type of drugs and certainly there is a good reason for broadening the scope of talks and the range of attendees from pure regulatory bioanalysis though to clinical chemists and maybe forensic sciences - indeed in the first few Reid Fora this was the case.

What will be the major themes of this year's Reid meeting? What do you anticipate might be the highlights?

I would like to feel that we are keeping abreast of the "usual" but also looking at the opportunities (and limitations) of enabling technologies in the Discovery arena and the developing MIST (metabolites in safety toxicology) issues – was it ever an issue or did the industry turn it into one, and last but not least – Dried Blood Spots – what are the financial benefits (pivotal) and improvements in Quality (fit for purpose) we can always add a decimal point to our data but to what benefit.

We have provided plenty of opportunity to discuss these issues and will be reporting back in the Special Edition of Bioanalysis dedicated to Eric Reid's memory.

Going beyond 2011, is there a future vision for the Reid Forum?

These are my personal views and as it will be my last Forum I can be a little more candid in my aspirations for the Forum.

Of late the industry has come to embrace the CRO fraternity, in larger number, an issue not lost on the Forum. It is important that the Forum does not descend into 10 CROs "seeking" business from 3 (2) major Pharma. I think the Forum exhibition sessions are something we have developed over the last few years giving exhibitors and delegates opportunity to discuss issues in depth. We continue to hold the price of the forum by moving from wine and silver service at lunch (for those that can remember) to Formica self service lunch while still maintaining the nature of the social sessions.

I believe the Forum needs to keep in touch with its constituency on a more regular basis and maybe link up with other groups such as the EBF could make this possible, developing a more professional approach to the organization (increased cost) of the meeting – however maintaining the essence of a meeting designed by analysts for analysts is essentially the way forward BUT can the time be found to do this?

Sounds like an all-consuming activity – do you have any time for other interests?

These include hill walking, gardening, antique and modern glass collecting as well as belatedly jogging, much against my logical sensibilities, except for the theoretical belief that fitness equal good health – last but not least travelling to visit the family diaspora now spread around the world.

Many thanks for your time, Howard. We wish you well with the Reid Forum (www.chromsoc.com).

There is much more to Howard Hill than being a leading light in the Reid Forum Syndicate. He joined HLS in 1999 as Director of Pharmaceutical Analytical Services and more recently as Group Director of Pharmaceutical Development. He has held a number of positions as Director / Head of Bioanalytical / Metabolism / Pharmaceutical Analysis in a variety of Contract Laboratories including IPHAR (Germany, Spain), BIOS (UK), BioResearch and Phoenix in Canada, Hazleton and Covance in the UK. Prior to his career in Contract Research he worked for Wellcome Laboratories, where he was a Post Doctoral Research Associate at the University of London, Middlesex Hospital Medical School and a Senior Analyst with Hoechst in the UK. He has authored over 200 papers, presentations and posters and co-edited the series "Methodological Surveys in Bioanalysis of Drugs" with Drs Reid and Wilson. He is past Chairman of the Joint Pharmaceutical Analysis Group of the Royal Society of Chemistry and the Royal Pharmaceutical Society (GB). He has a BSc and PhD (1971) in Biochemistry from the University of Wales and is a member of the Royal Society of Chemistry and American Association of Pharmaceutical Scientists. (Bio-details from Bioanalysis; Howard Hill is a Senior Editor of Bioanalysis, a journal of the Future Science Group)

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Biotechnology Journal, 2011.
Volume: 6 Issue: 4 Pages: 369-377

There are minimal regulatory influences on how you measure a broad range of molecules such as biologics. Although the FDA BMV Guidance provides guidance on the use of ligand based assays there is general acceptance that such assays, while more variable than LC-MS assays, can be made robust and reproducible. Much has been written about ligand based assays and will continue to be so apparently without a regulatory acknowledged consensus.

I think the word "must" is always fraught with difficulty in such a rapidly developing area and where the technologies used to measure them are developing equally as fast – the best that can be done is to set some criteria and issues that must be addressed to provide useful and relevant data using best practices at the time.

Are CRO's leaders in the field?

Biologics represent such a broad range of products and therapies that it would be difficult to say CROs were leaders in this field – I could say they have a broader range of experiences than Pharma who inevitably concentrate on certain areas of expertise and as such CROs are probably more experienced at putting together a broader range of development packages together. One of the objectives of the HLS Biologics meeting was to illustrate the diversity of approaches.

Historically there has been seen to be a "competition" between in-house and outsourced services – not unnaturally job preservation. This is breaking down; we all succeed together or fail together – models change and we must change to survive. Pressure to produce "cost effective" but still sophisticated therapies is becoming the norm.

Turning to the analysis of biopharmaceuticals, is it wrong to 'lump' all large biomolecules together or do different types present different problems?

It is definitely wrong to "lump" all "large" biomolecules together. Biologicals encompass a wide range of therapeutics, ranging from recombinant proteins which together with blood proteins represent the earliest group of biologicals, the peptide Insulin being the first such product. Next are the monoclonal antibodies which by number and sales are the biggest group of biological therapeutics followed by proteins, peptides, oligonucleotides, cell therapies, DNA vaccines and vaccines in general. These have been variously described as biopharmaceuticals, biotechnology products, biotherapeutics and last and perhaps most inappropriately bioceuticals or perhaps more appropriately biological therapies, many of the Advanced Therapies such as gene therapy and stem cells are complex not only in format but in the development process - our company has been involved in the development of one of the few gene therapies.

From an analytical perspective there are specific analytical challenges associated with different product types, ranging from vaccines where the objective is to generate an immune response, as such monitoring the presence of the "vaccine" is not a primary endpoint, through to evaluating protein structures that can be measured by LC-MS.

Biologicals now represent over 30% - 50% of all molecules in development. Biologicals are not new given that vaccines have been around for over 200 years, blood products such as clotting agents were developed in the last century and in the 1930s Insulin was identified, although it was not until Sanger developed amino acid sequencing in the 1950s that its structure could be fully elucidated.

The progress of Insulin as a therapeutic agent could be said to represent the history of biologics molecules. Although of unknown structure its purity was assessed using classical chemistry approaches e.g. crystallization while potency was a measured using *in vivo* methods of blood glucose lowering. Then later it could be quantified by ligand based assays (developed in the 1950s), only recently have the USP replaced *in vivo* assays with a chromatographic assay to measure Insulin purity and has the ability to separate it from closely related molecules like the desamido insulin.

Likewise *in vivo* measurement of blood kinetics for Biologicals relied largely on immunoassays the range of which has over the years reflected development in antibody production the main reagent in immunoassays, latterly chromatographic assay using LC-MS has been able to achieve sub ng/mL concentrations of insulin in blood driven by the development of insulin analogues with changes in their primary amino acid structure.

Turning to the Reid International Bioanalytical Forum, there seems to have been some confusion over the past year in UK "bioanalysis" meetings. Biopharmaceutical analysis meetings have included small molecule drug bioanalysis and vice versa. The Reid meeting has always ("eclectic mix" or not!) primarily been an analysis of drugs in biological fluids meeting. Will presentations on biopharmaceuticals only deal with the analysis of biopharmaceuticals in biological fluids?

An eclectic group of questions if I may say so, so lets try one at a time.

Some of this confusion arises from terminology as mentioned earlier Biologics and Biotherapeutics should be regarded as synonymous I see the term Biopharmaceuticals, (NOT biopharmaceutics, a different beast altogether) as a generic term for all therapeutic agents be they small molecules or large molecules.

Confusion is rife over terminology, Bioanalysis itself was coined over 30 years ago as the study of science used to measure drugs (of no fixed size) in biological fluids, by the way the Reid Forum and the proceedings generated by it went a long way to cementing this concept. However the terminology has been hijacked by the analytical science used to characterise biological molecules. That said there is a lot to be said for including as many sciences and perspectives in one meeting AND for getting the scientists to interact and get out of their silos.

The Reid Bioforum was always known for its unique character. Just how difficult has it been to retain some of that character that made the meeting so popular while still moving with the times?

I think this has been the biggest and continues to be the biggest challenge. The early meetings were ones where the big boss invariably attended and brought along his younger acolytes to share how they have solved problems in what was termed a "friendly" understanding environment. I think to some extent this has declined in the formal forum but the informal / social part of the meeting continues to be the arena for sharing best practices as such the "campus" nature of the meeting is integral to "encouraging" such discourse, although with the passage of time the use of student accommodation has lost favour with some – albeit with *en suite* accommodation as universal offering.

As an avowed anti-siloist, I feel that we should include everything from small molecules to large molecules from discovery assays to pivotal clinical bioequivalence assays. We need to break the barriers of Innovator Pharma to CROs, the former is a group I belonged to in the 1970s and where CROs were almost deemed to be pariahs. Now we have moved to a stage where CROs predominate where large Pharma are in the minority and mini/micro Pharma / biotech is a growth industry.

In addition we need now include biomarkers (as measures of PD), something the forum has being doing for over 15 years; after all, PK studies are surrogate for Response. I would like to see the Reid Forum as complimentary to the European Bioanalytical Forum, EBF – if there isn't a differentiator then its future is in doubt. If it does not develop a symbiotic relationship with the EBF then the Reid Forum needs to develop more presence than just once every two years e.g. with workshops on specific topics – this is especially so in a rapidly developing environment.

The Forum, held every two years over a four day period, has many disadvantages. Today two years can see the rise and fall of a new technology and four days can seem a lifetime – while problem solving and sharing problems can be done over the internet using such sites