
# Euro Exchange

Graham Hughes reports from the 25th annual DIA Euromeeting in Amsterdam that was held on 4th-6th March 2013

I calculate that this is about the 15th or 16th DIA annual meeting that I have attended. I took part in the first meeting at the same location, the RAI Conference Centre, and remember the few hundred delegates well and perhaps 30 exhibitors rattling around in the cavernous exhibition facility. Since then, the conference has grown significantly and has been located the length and breadth of Europe, from Lisbon to Copenhagen, London to Prague. It has now returned to the home in which it began in 1989 in Amsterdam.

This year there were over 2,000 registered delegates listening to speakers from the European Medicines Agency, the European Commission, the Food and Drug Administration and other national registration agencies. More than 200 exhibitors were in one of the largest exhibition floors in Europe.

## Diverse Content

The co-chairs of the conference proposed that, with a focus on better public health protection, greater transparency of the processes and the rational use

Images: DIA/Giles Ehrendtrandt

of medicinal products, the areas of discussion for the meeting would be classified into general disciplines, including pharmacovigilance (with the new European pharmacovigilance legislative framework in place for a year) and regulatory affairs for medicinal products and medical devices, R&D and clinical trials.

Other important topics covered included the Falsified Medicines Directive, the status of information for patients, the role played by scientific societies as experts and consideration over ageing populations, as well as paediatric studies. There were also student and professional poster sessions and presentations. The organisers hoped for the active involvement of patient organisations in addition to students and Fellows of the DIA.

The organisers had planned over 110 sessions divided into 19 streams. As usual, it was difficult for a general delegate such as myself to choose between the competing streams. This report covers the sessions that I personally found interesting, and I hope it provides a snapshot of the quality of the meeting and its content.

## CRA Role

The first session that I attended concerned new approaches to monitoring. Ken Getz from Tufts University Centre for the Study of Drug Development discussed the role of the clinical research associate (CRA) based on a snapshot survey carried out recently. This was the first survey of its kind and so did not address trends, but rather discussed behaviour. Getz' study revealed that:

- For Phase 1 studies, CRAs on average conduct 3.8 investigative site visits each month
- For Phase 2-3 studies, CRAs on average conduct 7.9 investigative site visits each month
- CRAs overall have an average of 6.3 years on the job and expect to remain in their position for another three years, with both metrics varying widely by region

The study also found that CRAs in clinical research organisations (CROs) work fewer hours than their counterparts in industry, and that the perceived quality of life of a CRA is relatively low in comparison to other healthcare professionals.

Risk-based monitoring is one of the hot topics of the day. Current economic conditions increasingly mandate that 100 per cent source document verification (SDV) is no longer feasible, and indeed no longer necessary, as was discussed by Rick Morrison from Comprehend Clinical in the US. Morrison contended that by identifying the correct triggers to justify site visits, not only could 30 per cent of the cost of monitoring the study be saved, but patient safety could also be improved.

This theme was taken up by François Beckers from GSK Vaccines, who noted that 100 per cent SDV by no means guarantees 100 per cent quality. In his company, much of the decision-making on frequency and type of visit is devolved to the CRAs themselves,



and they find that when using this approach 100 per cent SDV is necessary on only 10 per cent of subjects. These three lectures were followed by a lively question and answer session.

## Failing Trials

This track continued with a discussion of why clinical trials fail. This is against a background of an alarming increase in clinical development times of drugs over the past few years. The chairman of the session – Lollo Eriksson of Parexel – noted that 90 per cent of patients do not participate in clinical trials, only 10 per cent of doctors take part, and 50 per cent of sites underperform. Mary Jo Lambertie of Tufts Centre for the Study of Drug Development discussed a benchmarking exercise carried out by the centre. She noted that study duration is normally double what is planned, and highlighted contract review, regulatory constraints, protocol amendments, site selection difficulties, resources and availability of study materials as reasons for delays in clinical trials.

Perhaps surprisingly, the study found that traditional recruitment tactics, such as television and newspaper advertising, were still superior to the use of social media for patient recruitment. Moreover, virtually no retention incentive bore any fruit proportional to the dollars spent. Erica Buonansegna from the Technical University of Denmark also explored the failure of trials, noting that longer trials are often less successful. Efficacy and safety add up to the greatest reasons for failure, while administrative problems, such as protocol feasibility, low quality of data and complexity, also contributed to the failure of trials.

Jorge Mestre Ferrandiz, a senior economist at the Office of Health Economics in London, has examined the proposition that pricing constraints may inhibit the development of a second indication for a drug that is already on the market. The latest estimate of the cost of drug development by Paul *et al*

in 2011 is $1.8 billion, if failures are taken into account. He noted that since 2000, companies are increasingly focusing on high-risk, high-gain projects with relatively low expectation of success, but with greater rewards. This means that chronic diseases such as Alzheimer's, diabetes and rheumatoid arthritis, as well as lethal diseases like life-threatening infections and cancer, are being increasingly studied. His study has found that the pricing of a follow-on indication was not, counter-intuitively, a reason for the failure of a drug in a second indication.

### Antibiotic Debate

Several sessions addressed the problem of antibiotic resistance. I attended the session on 'Preserving What We Have – Prudent and Controlled Use'. The session chairman Richard Bergstrom, Director-General of EFPIA, introduced the concept that a scheme for approval and control specifically aimed at antibiotics was required. Professor Laura Piddock from Birmingham University discussed how to make prescribers aware of the problem. She pointed out that the cause of antibiotic resistance was due to their misuse, lack of new chemical groups, and the lack of the proper use of what we have. She maintained that the use of antibiotics underpins many lifesaving therapies, particularly for the elderly.

Other causes of the rise of resistance are over-the-counter availability, particularly in developing and southern European countries (compounded by the fact that many of these are counterfeit) and the use of antibiotics as growth promoters in animals, although this use is theoretically banned. She noted that antibiotic resistance may cost as much as $1.5 billion in the European Union (EU) alone and that in Africa antibiotic resistant bacteria kill twice as many children as malaria. The solution may arise as a targeted approach through the education of all users of antibiotics, from patient to consultant.

Bergstrom noted that the vast majority of antibiotics are prescribed by general practitioners who are often under pressure from patients themselves. The danger is that once a drug is approved, it is out of the control of the regulators, and so he proposed a compact between regulators, pharmaceutical companies, pharmacists, doctors, prescribers and even wholesalers to limit the use of antibiotics and prescribe them appropriately.

### Patient Involvement

The final session I attended on the first day concerned patient and consumer roles and their input into regulatory science. Peter Mol from the University of Groningen discussed a study he had conducted into the perception of risk by patients. The study dealt with two hypothetical drugs with different side-effect profiles and assessed the preferences of patients, their prescribers and regulatory assessors. Perhaps surprisingly, all three groups came to similar conclusions with respect to which drug they preferred, and were not persuaded that tiny risks, when doubled, were sufficient reason not to accept a particular drug.

Lisa Murphy from EURORDIS discussed how risk can be communicated to patients. She explained that patient advocates can reassure patients when drugs are alarmingly revealed to present dangers in the lay press. She told the audience that patients are now taking part more in risk assessment, along with regulators, but that risk perception by patients depends dramatically upon their disease. She felt that benefit and risk balance needs to be translated to patients in terms of quality of life, and emphasised that numbers are more important than percentages.

Several sessions addressed development of drugs for the elderly. In the first of these that I attended, Florian von Raison from Novartis explained how to optimise patient recruitment. He pointed out that at the present time it is not clear exactly what the definition of elderly is; is it over 65 or over 75? He said that in these studies, it will be necessary to have more women than men, since they represent a greater percentage of the elderly population. One consideration in such studies is that ethics committees should have specific training in elderly assessment studies, and that surveys should collect fewer data and be as small as possible in terms of patient numbers.

Valdo Arnera of PHT Corporation pointed out that patient recorded outcomes (PROs) are now part of 35 per cent of all studies. He felt that perhaps by 2025, 100 per cent of studies would include an element of PRO. One of his research projects considered the proposition that the elderly would be worse patients if such data were recorded electronically, yet found no difference between young and elderly patients in terms of accuracy or assiduousness in completion of PROs. Indeed, he found that the elderly

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preferred electronic methods to paper. Furthermore, he found that electronic PROs increased compliance with drug dosing. The final paper of this session discussed modelling and simulation in elderly patients, where it was felt that great benefit could be gained through the adoption of this technique more widely.


## Non-Clinical Issues

Rounding off the event, I attended sessions on new trends in *in vitro* non-clinical testing. This session provided an overview of exciting new and emerging trends in this area. Sonia Beken, a member of the Belgian Federal Agency for Medicines and Health Products, updated us on the acceptance of *in vitro* models bearing in mind the European Directive 2010/63/EU, which requires companies to use *in vitro* models where available. She drew the distinction between scientific and formal validation, which according to guidelines of 1997 must be reliable, as well as reproducible and predictable of human toxicology, but noted that new guidelines are under preparation to update these 16-year-old rules. Scientific validation is a different matter and merely requires the data to be reliable and reproducible.

Certainly, within the EU, considerable progress is being made towards the adoption of the philosophy of the 3Rs - replacement, refinement and reduction of animals in research. An application of this occurs in the recent ICH S10 photosafety guideline, which uses reconstructed human skin. Genotoxicity is also well along the line, though unfortunately there have been no formal validation studies in the area of liver toxicity.

Stéphane Dhalluin, Director of Investigational Non-clinical Safety at UCB in Belgium, gave a comprehensive review of where single cells are being used to give insight into human toxicity of drugs. Both embryonic stem cells and body stem cells can be used. Cardiomyocytes are now available commercially, although human hepatocytes remain very difficult to obtain. He set out the intriguing prospect of a 'lung on a chip', which consisted of lung cells on a membrane on the top of capillaries that could mimic inhalation toxicity studies. He said that liver and kidney cells on a chip were also in the pipeline. The final stunning possibility that he discussed was that of three-dimensional printers producing mimics of human organs for experimentation, if not for transplantation.

William Warren, a Vice President of a Sanofi subsidiary VAX Design in Florida, showed how the so-called MIMIC system could, by implanting and reproducing cells on a 3D scaffold, mimic the human immune system. The system could then be used to develop vaccines and possibly also look at the immunotoxic responses of other drugs.

Finally, I attended a session on carcinogenicity testing in animals, led by Jan Willem Van der Laan, a Senior Pharmacological Toxicological Assessor at the Netherlands Medicine Evaluation Board. He discussed how it may be possible to not carry out lifetime rat or mouse studies, except in cases where the outcome would be equivocal. Thus he felt that, if there was a high probability of human tumours being produced, such a study was not necessary and guidance being included on a future drug's label about such toxicity. The other class of compounds that he considered was one where there was no positive carcinogenicity at six months in animal studies, and when no genotoxicity had been noted.

That just left the uncertain products. It was surprising to hear that some 50 per cent of compounds currently on the market are positive in either rat or mice lifetime studies. Apparently, rats predict very poorly which organ is susceptible to tumours in humans, although the overall susceptibility prediction is good. Likewise, a negative result in a lifetime study in a rat is also a reliable predictor. These new approaches to toxicity – cell-based, model based and knowledge based – give added impetus to the adoption of the 3Rs principle.

## Conclusion

Overall, the DIA was an interesting and useful conference for me. As usual, there was much in the regulatory arena for those whose metier is in that direction, and it certainly gave a valuable update of EU legislation and recent initiatives to those requiring one. It was very interesting to see a large number of recently formed CROs and other vendors in the exhibition hall. Conspicuous by their absence were most of the major CROs. The venue is by no means ideal for a conference of the size of the DIA, but the conference itself was well worth attending.