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Topic: Pharmacovigilance in the Future

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Good afternoon Ladies and gentlemen.

First of all, let me thank you for asking me to give this talk at the 10th anniversary conference.

Secondly, I like to wish the EMEA a happy 10th anniversary.

I have been asked to focus my talk on Pharmacovigilance. I am going to focus on how we will need to handle Pharmacovigilance in the future; clearly this is very much a personal perspective, but I hope you agree with at least some of the sentiments that I will express.

Before I focus on the future, I really have to give you a perspective of where we are at the moment.

Let me start off with the definition of Pharmacovigilance. This is science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems. This is the WHO definition. There are many different aspects to this definition:

- **detection**: this is the process whereby we detect the occurrence of adverse effects associated with drug therapy. Clearly different methods are used at different phases of drug development. By the time a drug is licensed, we will only be aware of some of the common adverse effects, and most of adverse effects are identified after licensing.

For this, we rely on various methods including spontaneous reporting systems, traditional epidemiological methods, and increasingly now, record-linkage databases.

- **Evaluation** should include analysis of the strength of evidence and clinical relevance of the findings;
- **prevention**, usually deals with communication with prescribers and patients and application of the evidence of risk in order to improve the public health.

In my opinion, these different aspects of Pharmacovigilance will have to change in the future, and encompass many of the advances that are currently happening and others that are likely to happen in the near future.

So where are we at present with regard to Pharmacovigilance? Adverse drug reactions clearly still represent a major clinical problem. The whole issue of drug safety is very much in the public eye at present. We have had major safety problems over the last year, which have included psychiatric adverse effects with the SSRIs, and more recently, thrombotic complications in patients on COX-2 inhibitors. Recent data from the FDA, published in the Lancet, suggested that over 100,000 extra cardiovascular events may have occurred in the US population because of the use of rofecoxib. If we go back a few years, an analogous situation arose with terfenadine. Again, data from the FDA, suggested that 7 1/2 million people were exposed to terfenadine before any regulatory action was taken. Therefore Ladies and gentlemen, my question to you is: how long can we continue in this vein?

Adverse drug reactions continue to be a major cause of hospital admission and occur in hospital after the patient has been admitted for another condition. The highly publicised meta-analysis by Lazarou published in the Journal of the American Medical Association

suggested that ADRs were between the fourth and sixth commonest cause of death in the USA in 1994. A study we published last year in the BMJ showed that adverse drug reactions continue to be a major burden, and support the claims made by Lazarou. In a prospective six-month study which looked at 19,000 admissions, we were able to show the 6.5% of all admissions were due to adverse drug reactions. If this is extrapolated to the whole NHS bed-base, it is likely that there are seven 800-bed hospitals currently being occupied by patients with adverse drug reactions. The cost of this to the UK healthcare system is at least £0.5 billion per year. The death rate due to ADRs in our study was 0.15%, very similar to the 0.14% suggested by Lazarou.

Clearly, what I have just said is not to decry what has already been achieved in the field of Pharmacovigilance over the last 40 years since the thalidomide disaster. We now pick up many drug safety signals much earlier than they would have been without the current processes, and many lives have undoubtedly been saved by the process of Pharmacovigilance. However, there is always room for improvement, and all regulatory agencies, drug industry and researchers must look for new methods to improve drug safety and protect public health. This will necessitate an understanding and embracement of the new technologies.

What I would like to do first of all is to concentrate on information technology. We currently rely on spontaneous reporting of adverse reactions by healthcare professionals. These are then stored in bespoke databases such as the ADROIT database in the UK, the WHO database in Uppsala and the new EUDRAVIGILANCE database. These are clearly valuable resources, and help to pick up signals of ADRs. However a major problem with all such schemes is the degree of under-reporting of ADRs. Even with fatal reactions, less than 1 in 10 reactions may be reported. Imagine a system where every adverse reaction can be reported and recorded.

Clearly with the advances in computer technology, this is possible, and is likely to happen in the future. In the UK, there is currently a drive to introduce uniform computer system in the whole of the NHS. This will lead to a single patient record and single medication record – this will allow clinical events to be linked to drug prescriptions, and when an ADR occurs, for this to be automatically recorded. This would not only allow almost complete ascertainment, but will also allow us to pick up new signals, characterise existing signals more rapidly, and define risk factors, and so on. This clearly requires a lot of resource, but if one was to look in the future, it may turn out to be very cost-effective through prevention of morbidity and mortality. Since this is the EU, and all member states should be working in co-operation, the ideal situation would be the whole of the EU member states to operate on similar systems – clearly, this seems unimaginable at present, and political, resource and patient confidentiality issues may prove to be insurmountable barriers, but we should nevertheless try.

Whatever system is developed in each member state in the future, success in improving pharmacovigilance in the EU will depend on how thought has been put in to develop the systems. Let me highlight two areas. First, any systems that are available must be able to talk to each other, i.e. compatibility is essential. Second, they must be designed intelligently so that information is gathered efficiently, but as important will be the ease with which we can retrieve the information and link drug prescription to clinical outcomes. There are many existing databases from which any new systems have to learn from and improve. However, it is important that this does not lead to abandonment of the existing databases. Such databases (although only covering a proportion of the population rather than the whole population) need to be maintained and strengthened while any new databases are being assembled. A typical example here is the GPRD which has been of immense use, and is used by all regulatory agencies and Pharma worldwide.

With any system that builds on information technology, we need the co-operation of the consumers, i.e. the patients. By not keeping them included and informed, will lead to suspicion. It is therefore essential that any systems are transparent, and patients need to be included as partners in their own healthcare.

Let me now turn to the emerging biotechnologies. We currently prescribe drugs on the basis of one dose fits all, irrespective of the age, sex, ethnicity of the patient. However, we know that patients vary in their responses to drugs, with some developing adverse reactions. It has been known for a long time that the genetic constitution of the patient influences the response to the drug – this is the field of study known as pharmacogenetics or pharmacogenomics. This is not a new field; the name was first coined by Vogel in 1957. However, the human genome project has added impetus to this area of research. The sequencing of the human genome is one of the greatest scientific advances ever. We know that 99.9% of the human genome is identical; variability is seen in 0.1% or 3 million bases, and this is enough to account for the diversity of the human race, which is essential for the survival of the human race. This variation is also responsible for the way in which we respond to drugs, at least partly.

Pharmacogenetics holds the promise of being able to reduce drug-related morbidity. There are already some examples of where knowledge of the patient's genotype can predict susceptibility to an ADR. For example, the enzyme TPMT shows a trimodal distribution in the human population with 1 in 300 people lacking the enzyme and 10% having intermediate values. Both groups of patients (i.e. those that are completely or partially deficient) require lower doses of drugs such as 6-mercaptopurine. Use of conventional doses of 6MP in TPMT

deficient patients will lead to bone marrow suppression. Cynics will comment and state that this is the only example that people use, and there are very other success stories. They are partly correct.

We know that pharmacogenetics has not yet reached clinical practice to any great extent. One of the main issues we have to face up is that drug response is not simple, but is a complex multifactorial process, which very much like complex diseases, depends on the interplay of multiple genes interacting with environmental factors. This is where we have to change our stance from one of pharmacogenetics (looking at single genes) to pharmacogenomics (looking at the whole genome) – the availability of the genome sequence together with rapid advances in technologies that are occurring will allow us to do that. Over the last few years, there have already been some advances – in the area of ADRs, abacavir hypersensitivity represents an important paradigm. ABC hypersensitivity occurs in 5% of patients given the drug. Analysis of the genetic predisposition using patients from Australasia, North America and Europe has shown that HLA B57 acts as a major predisposing gene – a pooled estimate suggests that possession of B57 will increase the risk of hypersensitivity by 29-fold. Estimates from Australia suggest that the incidence of hypersensitivity has gone down from 8% to less than 2%. An analysis that we have undertaken shows that pre-prescription genotyping for B57 may also be cost-effective.

It is important to note that this test is not 100% predictive (it displays a positive predictive value of 82%). Because of the complexity of drug response, I think it would be very optimistic to expect 100% predictivity with any pharmacogenetic test. If clinicians, regulators and patients have this expectation, then pharmacogenetics will fail – no doubt about it. Certainly some focus groups have shown that there are unrealistic expectations as to what

pharmacogenetics can achieve. Therefore the use of any pharmacogenetics test must be accompanied by education of the prescriber and of the patient on what to expect and what not to expect.

There are many obstacles to be overcome before we can bring genetics into clinical practice. Most importantly we need to gather the evidence. We need better designed studies, which may for common adverse events, have to be prospective in nature so that one can take into account the environmental factors and look at the interaction between nature and nurture. Given that most of the drugs that we use are old drugs, and out of patent, the funding to undertake these studies will necessarily have to come from the public purse. There are many important areas I could go through with respect to the future success of pharmacogenetics, but I will restrict myself to two more areas:

1. the need for facilities for sample collection from patients. We need to use all methods that are available to ensure that we can do this effectively and efficiently – this is going to be particularly important for rare adverse events.
2. Any studies clearly have to be done within an ethical framework and with due regard for patient confidentiality. However, we should also ensure that any regulatory processes are not overly burdensome, as this will deter research. We need more streamlined regulatory processes – a one stop shop where everything is satisfied through one form and one set of questions, not the multitude of forms that need to be filled out now. Let me give you an example: for a study on drug-induced hepatotoxicity in the UK, once we have got ethical approval, we are currently having to go around 100 different hospitals to get individual approval, and none of these departments seem to have any standardisation. The burden of execessive regulation is

already having an effect on research in the UK – ethics committee submissions are down this year.

Clearly with pharmacogenetics we are looking at a static end-point. That is, a germline polymorphism will be present from birth to death. However, our cells, organs and the body represent dynamic systems which are constantly changing and adapting to the environment. Therefore any response to a drug may also have to take account of these processes. Again, technologies are available here. To look at protein patterns in the body, we can use proteomic technologies, while metabonomics looks at the pattern of metabolites in body fluids and how they change in response to drugs. Let me give you an example of the potential power of the latter: in patients with IHD, it was possible through analysis of metabolite patterns in human serum, to distinguish between patients with normal coronary arteries and those with triple vessel disease with a specificity greater than 90%. That is a very impressive result and highlights the potential power of the technique.

We are developing all these technologies, and there is no doubt that they are getting cheaper. However, for them to be successful, they need to be easily incorporated into current clinical practice. They need to be amenable to the general practitioner who has 7 min to see a patient, and cannot possibly be expected to become an expert in all aspects of human genetics. This brings me back to the power and usefulness of information technology. We are going to generate a lot of data with these biotechnologies – let me give you an example: currently there are gene chips with which you can simultaneously look at 500,000 gene variants. Potentially this will provide you with 500,000 data points on each individual. If you are doing a study in 1000 patients, for example to identify predisposing factors, 5×10^8 data points. Such data will need to be gathered, harnessed, and interpreted. This field of bioinformatics is therefore

going to be absolutely crucial. Data that is gathered through these technologies will have to be translated into a form that is understandable by the prescribing clinician. This will require the linkage between bioinformatics and health informatics, and as you can imagine, this in itself is going to be a major challenge.

Ladies and Gentleman. To conclude.

I have given you a brief tour of the problems that we are currently facing with respect to drug safety issues. For the future, we need to embrace all the available and the emerging technologies so that we can make drug therapy as safe as possible and thereby protect public health. However, it is not going to be easy. There are many obstacles to be overcome, some of which I have gone through. In the end, this is going to require a concerted effort from all stakeholders including patients. The sooner we begin to tackle these issues, the quicker we will get there. Thank you for your attention.