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Pharmaceutical Medicine

*The Society of Pharmaceutical Medicine
in association with the International Federation
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Meeting Report
2008 ICPM Meeting

The 15th International Conference on Pharmaceutical Medicine

7–10 September 2008; Amsterdam, the Netherlands

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The International Conference on Pharmaceutical Medicine (ICPM) is organized by the International Federation of Associations of Pharmaceutical Physicians (IFAPP), in collaboration with one of its member organizations. In 2008 the event was held in Amsterdam under the guidance of the Dutch Association of Pharmaceutical Medicine – Nederlandse Vereniging Voor Farmaceutische Geneeskunde – on 7–10 September.

The theme of this year's ICPM was "Developing Pharmaceutical Care, Medicines after the Blockbuster Era" and the meeting contained a mix of scientific and market-related topics in the field of pharmaceutical medicine.

The venue for the meeting was the Hotel Okura in the southern part of the city and some 240 professionals from both industry and academia attended the event. In addition, there were 15 exhibiting companies and a selection of poster presentations on offer, addressing various facets of pharmaceutical medicine from educational offerings to IFAPP global strategy.

1. Opening Ceremony

Before the conference proper, attendees were invited to partake in a boat ride along one of the city's numerous canals, followed by a welcome reception at the renowned Rijksmuseum, the largest museum in the Netherlands. The event was an opportunity for friends and colleagues from all over the globe to gather and discuss the latest happenings in the field of pharmaceutical medicine. They were joined by two distinguished speakers – *Dr Rien Meijerink*, Chairman of the Dutch Council for Public Health and Health Care, and *Professor Kees van Grootheest*, Director of the Netherlands Pharmacovigilance Centre Lareb – who gave their views on the importance of establishing trust in the pharmaceutical industry and in medicines in general.

The following meeting report overviews a few of the many sessions that were available during ICPM 2008.

2. New Paradigms in Research and Development

Discussing the topic of translational medicine in exploratory development, *Dr Andreas Wallnoefer* from F. Hoffman-La Roche described the new development structure being used at the firm to try to improve the efficiency of the current research and development (R&D) process and increase the number of new medicines reaching the market; in effect, moving away from serendipitous discovery and towards enhanced predictability.

The cornerstones of the new system are disease biology leadership teams (DBLTs) and the formation of a Clinical Research and Exploratory Development (CRED) function, with the aim of generating knowledge and understanding of disease biology across the whole value chain of pharmaceutical R&D.

In the Roche model, there are four pillars of innovation in clinical research. The first is translational medicine, to translate preclinical science into the clinical setting and feed clinical information back into the discovery programme. Translational medicine is the focus of CRED and fundamental to developing an understanding of disease as the molecular science and physiology underlying the pathology, said *Dr Wallnoefer*. Clinical trials are also designed and initiated earlier in the relevant patient populations.

The second pillar is system biology, to understand the complexity underlying the disease. Third is modelling and simulation, to analyse, understand and predict data. Finally, biomarkers are needed to understand the mechanism of action of new drugs and the targeted disease, and to aid decision making. This fourth pillar is a key tool and a central element throughout the life cycle of a medicine; critical for both translational medicine and explore and confirm development strategies. This work can lead to improved decision making in R&D, better understanding of pathways and mechanisms, and act as a driver for pharmacodiagnostic development.

To use oncology research as an example, Roche is now moving away from the old R&D paradigm, which focused on toxic, non-selective chemotherapy drugs, and moving towards targeted therapies using molecular biology discoveries from the 1980s. In the future, this move is expected to lead to the integration of molecular diagnostics with targeted therapies to characterize individual cancer types and provide tailored care to oncology patients.

As part of his presentation, Dr Wallnoefer reminded the audience of the quote from renowned physicist Dr Albert Einstein, which seemed apt for the current conundrum facing the industry – “Doing the same thing over and over again, yet expecting different results, is the definition of crazy.”

3. Biomarker Validation

Returning to the topic of biomarkers, *Dr Paul Rolan* from the University of Adelaide in Australia tackled the issue of validation. As was clear from the conference as a whole, biomarkers have come of age in the 21st century and are now an essential part of the R&D toolkit, with uses crossing the spectrum from pharmacokinetic and pharmacodynamic modelling to efficacy and safety assessment. But a vital question to ask is “can we assess the confidence we have in the prediction?”

Two areas must be considered for this – is the measurement correct and what interpretation can be made from that measurement? For this interpretational element of validation, there are in turn four key aspects to consider.

The first aspect is criterion validity or “how does the test compare to the gold standard?” (for example, a clinical endpoint). For this, one must remember that we are looking at a statistical association rather a scientific, causal link.

Secondly, construct validity should be assessed by asking “is there an accepted theory to link the test used and drug effect sought?” If a genetic marker displays a strong statistical association with an outcome but we have no mechanistic reason to underpin the association, then validity will be poor. Because this aspect of validation is based on current scientific knowledge and

belief, it is obviously highly changeable and vulnerable to new information. Hence, construct validity is time dependent and should be viewed as somewhat subjective. It depends upon the exact question being asked and is context dependent. It also does not establish a mechanistic basis for the biomarker.

Thirdly, face validity plays a part – “does the test appear to be a plausible measure of the drug effect sought?” An example would be a driving test on the road being a better measure of impaired driving ability than a laboratory-based tracking test.

Finally, content validity should be considered when using test panels, to confirm that the panel covers the range of intervention effects sought.

The different types of biomarkers will assign different relative importance to these four aspects of validation. They may be drug specific to assess the pharmacological effect of the drug or they may reflect a system property when the test drug has a subsequent effect on the disease mechanism (see table I). The former type of biomarker is easier to validate than the latter and more likely to be studied by a pharmaceutical company as part of its development programme. The second type of biomarker, looking at biological response, and system- rather than drug-specific, is more likely to be validated by academic institutions than individual pharmaceutical companies.

When no appropriate biomarker is currently available, its development should occur in parallel to the animal programme with the ultimate goal of developing a marker that can be used in both animals and man, and can link the data from these studies.

Dr Rolan finished his presentation by asking the audience to change their question from “has the test been validated?” to one that asks “to what degree has this test been validated, for this purpose, in this population and in this environment and, finally, how can this information be used to make decisions?”

4. Adaptive Trial Design

Looking at the role adaptive trial designs may play in reinventing pharmaceutical R&D, *Dr Kit Roes* described such designs as

Table I. Differences between biomarker types

Descriptors	Biomarker type 1	Biomarker type 2
Target measurement	Pharmacological effect of the drug	Biological or disease response
Outcome	Confirm or refute preclinical predictions and assess the pharmacodynamic/pharmacokinetic relationship	Measure a downstream effect of the primary pharmacology (that is likely to result in clinical benefit)
Surrogate marker potential	No	Yes
Specificity	Drug-specific	System-specific
Relative ease of validation	Easy	Hard
Likely to be validated by	Pharmaceutical company	Academic institution

the “Holy Grail” of clinical research, effectively allowing researchers to learn as they go, implement mid-trial design modifications, increase their probability of success and still end up with a valid clinical trial. These trials are more ethical because they expose fewer patients to ineffective or unsafe drugs, more efficient because valuable resources can be directed into the most promising candidates for future development, better because they allow us to learn as the data accumulate and faster because previously separated stages of development can be merged.

Adaptive trial designs have been around for many years but, in 1994, an alternative approach known as adaptive interim designs was proposed, the basic statistical principle of which is very simple. These designs effectively split the study into two parts, the data from which can be combined at the end of the trial or, alternatively, one part can be stopped if clear disadvantages are seen in the interim analysis.

Whereas non-adaptive study methods include long periods of information ‘blackout’ while trials are in progress, adaptive trial designs effectively allow us to create a window into the drug development process to see how things are progressing. This offers the opportunity to adjust the study dose or explore additional doses, make minor adjustments to the study design and to stop the trial early on the grounds of futility.

Outlining the regulatory agencies attitude to adaptive trial designs, Dr Roes said that the potential benefits of these methods are being recognized but that regulators are taking a cautionary approach, particularly in the confirmatory stages of development. The rationale for these studies must go beyond “faster and more efficient” to that of providing scientifically better answers. The issues involved in these studies, such as the risk of introducing bias by conducting interim analyses, must also be addressed. Thus, adaptive trial designs may be of greatest value in the proof of concept stage of drug development.

5. Evidence without Label

To address the topic of off-label pharmacotherapy, *Professor Anthonius de Boer* from the University of Utrecht in the Netherlands began his talk by quoting figures from a study by Radley and colleagues^[1] that found that of 160 commonly prescribed drugs that were assessed, 21% were prescribed off-label and 73% of these had little or no scientific evidence to support their use. Furthermore, for children who are treated in hospital, this figure may be as high as 60–90%.

Advantages of off-label drug use include the ability to innovate, gain early access to potentially valuable medications, allow the adoption of new practices based on emerging evidence and to provide the only treatment option for certain orphan indications.

On the other hand, off-label use can undermine expectations that the benefit-risk balance of a drug has been fully evaluated. Furthermore, off-label pharmacotherapy may result in increased health care costs, undermine the incentives for drug manufacturers to perform rigorous studies, support the seeking of approval in secondary indications for which development is less complicated and expensive, discourage evidence-based practice, and result in under- or over-administration because these drugs lack dosage schemes.

While off-label pharmacotherapy is legal, the US Food and Drug Administration (FDA) does regulate the promotion of such use, although the rules change periodically. The FDA Modernization Act of 1997 permitted sponsors to disseminate peer-reviewed studies when the drug had been or would form part of a supplemental new drug application (sNDA). However, this law expired in 2006 and it became prohibited for sponsors to promote any off-label use. In 2008, draft guidelines were released by the FDA that would allow sponsors to distribute articles containing off-label information provided that the publication in which those articles were originally published has an editorial board, uses independent peer reviewers and has a policy of full disclosure of conflicts of interest. In addition, the study design has to be adequate and well controlled, and the article may not form part of a sponsor-funded journal supplement.

Professor de Boer suggests that off-label drug use is only acceptable when no alternative authorized drug is available or the benefit-risk profile of the off-label agent is better than the alternative approved drug, when there is solid scientific evidence to support efficacy, when such use is supported by professional guidelines and standards, and when informed consent is obtained from the patient. Furthermore, when assessing the available evidence for off-label use, publication bias must be considered because negative trial results are often not published.

6. Risks Associated with Off-Label Drug Use

To clarify the European Medicines Agency’s (EMEA’s) position on off-label pharmacotherapy, *Dr Noel Wathion* explained that the agency tries to provide a balance between wanting to protect patients from ineffective medicines and allowing doctors to use their own clinical experience to treat patients. Off-label use is a reality because clinicians are often aware of ongoing clinical trials in new indications and there is often inadequate information in special populations such as children and pregnant women. However, doctors must be aware that off-label prescribing carries the risk of liability because no formal ‘assurance’ of a positive benefit-risk balance has been given.

In 2005, Risk Management Plans (RMPs) for approved indications were introduced in the EU as part of the marketing authorization application for new active substances. RMPs are defined as a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

There are two parts to a RMP. The first is the Safety Specification, which should describe the known and potential risks of the drug, including the risks associated with off-label prescribing, and also outline any missing data. This section contains the Pharmacovigilance Plan, which describes what activities are necessary to identify and characterize these risks. The second part is an evaluation of the need for risk minimization activities. If the need for additional activities that go beyond information to be included in the product label is confirmed, a Risk Minimization Plan will also need to be submitted. Examples of such activities include controlled distribution of the drug, educational material for prescribing physicians and patient alert or monitoring cards.

Dr Wathion explained that the EMEA is particularly concerned about off-label use when the drug has the potential to induce serious adverse reactions that require additional risk minimization activities, has abuse or misuse potential, carries particular hazards when used outside the approved indication or when the medicine has only had very limited exposure in the clinical trial setting and the safety profile is not well known.

Off-label use of orphan drugs is a particular concern because of the propensity for limited safety information given the small numbers of patients enrolled in the pre-authorization trials. Paediatric off-label use is another area of concern given, among other issues, the pharmacokinetic and pharmacological differences between adults and children. An assessment of paediatric off-label use is now a mandatory part of RMPs.

In closing, Dr Wathion told the audience that we need to better anticipate the potential for off-label use during the pre-authorization phase of drug development in order to document its importance and the potential consequences of such use, particularly in the early post-marketing phase of the drug's life cycle.

7. Launch of the Dutch Medicines for Children Research Network

The official launch of the Dutch Medicines for Children Research Network (MCRN), which was chaired by *Professor Martin Offringa*, Director of MCRN, was very well attended by conference participants and the press. The organization is dedicated to promoting and facilitating paediatric drug development in order to ensure the safety and efficacy of drugs used to treat this special

patient population. The Network comprises all hospital facilities, academic and non-academic, that care for sick children in the Netherlands.

During the launch, *Dr Louise Gunning* from the Dutch Federation of University Medical Centres spoke about the difficulties associated with exposing children to the clinical trial setting, knowing that by the end of the trial one group is likely to have received less effective treatment than the other. However, Dr Gunning pointed out that the alternative is to allow this situation to continue *ad infinitum* if we are unable to gather the information needed to truly assess the effectiveness and safety of medicines in the paediatric population.

The MCRN supports both industry-sponsored and investigator-initiated studies in the Netherlands through its infrastructure, which comprises the Dutch Coordinating Centre, Regional Research Clusters, Clinical Studies Groups and a National Trial Support Unit. Additional information about the Network can be found at <http://www.mcrn.nl/>.

8. Nanotechnology as a Driver for Pharmaceutical Medicine

One of the topics identified as a key scientific drivers for the future of pharmaceutical medicine at this year's ICPM was pharmaceutical nanotechnology and *Professor Sandy Florence* from the Centre for Drug Delivery Research at the University of London in England, began his discussion by outlining broad areas in which nanotechnology may prove valuable in the future, such as facilitating improved drug outcomes, reduced adverse effects, new diagnostic and tracking systems, more personalized medicines and realizable gene delivery.

In reality, the term nanotechnology refers not to one but to several different technologies, including nanomaterials, nanodevices and nanosystems. Professor Florence explained that while small systems are not in themselves innovative, nanoparticles (i.e. particles that are less than 100 nm in width) have the potential to reach sites that larger molecules cannot and via routes that cannot be accessed by microparticles. Such potential has therapeutic, diagnostic and toxicological consequences, and nanopharmacy is vital in providing the tools for nanomedicine to make such advances.

Furthermore, nanosystems come in a range of sizes and shapes. In addition to nanoparticles, there are nanotubes, nanocrystals, dendrimers and quantum dots. The latter, for example, are semiconducting nanocrystals, typically of 2–10 nm in diameter, that fluoresce when they are excited by a light source. Biomedical application of these quantum dots may extend to *in vitro* imaging of fixed cells and tissues, intracellular organelles and membranes;

in vivo targeting of cells, tissues, organs and tumours for diagnosis, therapy and testing; bioanalytical assays such as fluorescence-activated cell sorting and microarrays; and other as yet unknown applications in the fields of biosensors and drug delivery.

Professor Florence stressed that while much is possible, we are not there yet and care needs to be exhibited. Inherently nontoxic materials might become toxic when in nanoparticle form, partly through changed energetics at the surface of the particle and partly because of their ability to reach areas of the body that larger molecules cannot. In his view, hybrid systems, which could be used to deliver drugs encapsulated in nanoparticles to a specific target, will be the first nanotechnology devices to achieve widespread use. Nanofabricated devices may follow and perhaps the use of biological templates such as viruses for fabricating delivery devices for drugs and diagnostics. Professor Florence concluded his session by saying that nanotechnology has much to offer the pharmaceutical industry but even more to prove.

9. Personalized Medicine

The last talk of the meeting was given by *Professor Michael Liebman*, the Managing Director of Strategic Medicine Inc., on the subject of personalized medicine. Like many others, and in line with the theme of ICPM 2008, Professor Liebman believes that we are reaching the end of the blockbuster era. Moving ahead, personalized medicine presents an opportunity to develop innovative medicines that specifically target individuals with the most to gain from such therapies and, in doing so, shorten the drug development cycle and generate revenue earlier in the process than is currently possible.

The traditional view of personalized medicine is that we use information about a patient's genotype or gene expression profile

to tailor their therapy. However, Professor Liebman expressed the view that this concept should be expanded to one of personalized healthcare, which incorporates the patient's lifestyle and environmental influences, as well as the natural history of their disease.

In this respect we must change our thinking to view disease as a process rather than a state, said Professor Liebman. If we want to understand the disease, we must understand the patient's clinical history. This, in addition to our increasing understanding of the complex biology that perturbs normal function and results in disease, should lead to stratification of the disease early in the discovery phase and stratification of the patient early in the development process. This stratification is the first step towards personalized medicine. From there, the future and ultimate success of the discipline lies in forming and optimizing partnerships between the pharmaceutical industry, the physician and the payer, with the patient as the central focus.

10. Singapore 2010

Finally, to mark the end of an educational and thoroughly enjoyable meeting, *Dr Jean-Paul Deslypere* took to the podium to give a brief overview of the next meeting, which will be held on 7–10 November 2010 in Singapore. ICPM 2010 will be held in collaboration with the Association of Pharmaceutical Physicians, Singapore of which Dr Deslypere is President.

More information on the event can be found on the IFAPP website at <http://www.ifapp.org>.

Reference

1. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006; 166 (9): 1021-6