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Workshop on pharmacogenomics: from science to clinical care

Report

Report of the workshop held on 8-9 October 2012 at the European Medicines Agency



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Workshop on pharmacogenomics: from science to clinical care

Workshop report

Disclaimer

This report was sponsored by the European Medicines Agency in the context of the Workshop on pharmacogenomics: from science to clinical care. Although the conclusions it contains have been endorsed by the Agency, the views expressed are those of the authors and do not necessarily represent an official position of the Agency.

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1. Agenda

Pharmacogenomics has become an actual scientific application in drug development and evaluation. A number of medicinal products based on pharmacogenomics have been developed by the pharmaceutical industry, submitted to the Agency for scientific advice or for Marketing Authorisation and are made available to the patients across Europe and globally.

Pharmacogenomics is also emerging as an important tool in the evaluation of serious adverse reactions experienced in clinical care.

Objectives of the workshop

- To share international expert views on pharmacogenomic applications in clinical development, the evaluation of marketing authorisations and patient's access to medicines.
- To discuss challenges and bottlenecks.
- To identify areas for regulators and other stakeholders' joint actions.
- To serve as a training forum for senior assessors of the EU expert network.

Outcome of the workshop

The workshop provides for a full picture of the impact of genomics in the scientific landscape of medicines' development as well as in patient care and health care aspects. It became evident that genomics is internally part of drug development as appropriate in early phases but also based on re-definition of diseases at molecular level in applied care. The areas identified for collaboration included cooperation among regulators of different health products and health services critical for the delivery of stratified and in the future personalised medicine and also prompted for a transformation of the current paradigm, not only for drug development but also for therapeutic approaches whereby a more precise treatment impacting on the mechanism of disease would allow for better prognostic as well as predictive approaches.

Organising Committee

Tomas Salmonson, Medical Products Agency, Sweden

Krishna Prasad, Medicines and Healthcare Products Regulatory Agency, UK

Agnes Saint Raymond, European Medicines Agency, UK

Marisa Papaluca, European Medicines Agency, UK

Falk Ehmann, European Medicines Agency, UK

Programme Chairpersons and Co-chairpersons:

Session 1: Krishna Prasad, Medicines and Healthcare Products Regulatory Agency, UK

Falk Ehmann, European Medicines Agency, UK

Session 2: Robert Hemmings, Medicines and Healthcare Products Regulatory Agency, UK

Francesco Pignatti, European Medicines Agency, UK

Session 3: Isabelle Moulon, European Medicines Agency, UK

Krishna Prasad, Medicines and Healthcare Products Regulatory Agency, UK

Session 4: David Haerry, European Aids Treatment Group, Belgium

Marisa Papaluca, European Medicines Agency, UK

Session 5: Tomas Salmonson, Medical Products Agency, Sweden

Jane Moseley, European Medicines Agency, UK

Session 6: Stephen Spielberg, Food and Drug Administration, USA

Emer Cooke, European Medicines Agency, UK

List of speakers

Frédérique Nowak, French National Cancer Institute, France

Federico Goodsaid, Vertex Pharmaceuticals, USA

Marc Maliepaard, Dutch Medicines Board, the Netherlands

Michael Pacanowski, Food and Drug Administration, USA

Krishna Prasad, Medicines and Healthcare Products Regulatory Agency, UK

Martin Posch, University of Vienna, Austria

Viswanath Devanarayan, Abbott Laboratories, UK

Peter Arlett, European Medicines Agency, UK

Qun-Ying Yue, Medical Products Agency, Sweden

Isabelle Moulon, European Medicines Agency, UK

Hans Georg-Eichler, European Medicines Agency, UK

David Haerry, European Aids Treatment Group, Belgium

Robert Diasio, Mayo Clinic Cancer Center, USA

Ronald van Schaik, Erasmus Medical Center, the Netherlands

Fabio Faraulo, European Commission, Belgium

Stuart Hogarth, King's College, UK

Elisabeth George, National Institute for Health and Clinical Excellence, UK

Adrian Llerena, CICAB University hospital, Spain

Yoshiaki Uyama, Pharmaceuticals and Medical Devices Agency, Japan

Steven Lewitzky, Novartis, Switzerland

Tomas Salmonson, Medical Products Agency, Sweden

2. Abstracts

Session 1: Pharmacogenomics: regulatory and methodological implications in early clinical development

Chairperson: **Krishna Prasad**, Medicines and Healthcare Products Regulatory Agency, UK

Co-chairperson: **Falk Ehmann**, European Medicines Agency, UK

"Pharmacogenomics in Rare Diseases: Development Strategy for Ivacaftor as a Therapy for Cystic Fibrosis"

By **Federico Goodsaid**, Vertex Pharmaceuticals, USA

The development of novel therapies for rare diseases and personalized healthcare share many similarities. One of the most important ones is the limited number of patients available for therapeutic product development studies with rare diseases and personalized healthcare. The numbers of patients may be so small, that the strategies for clinical study design need to integrate novel studies which have a sound scientific rationale and robust statistical structure. There are several issues to be addressed, including the definition of clinical study population classes on the basis of molecular or clinical phenotypes, and response variability driven by differences in specific mutations associated with molecular defects in a disease. In the end, a question should be asked with some urgency: *are we ready to draft a guidance on best practices in the design of clinical studies for rare diseases and personalized healthcare?*

"Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products"

By **Marc Maliepaard**, Dutch Medicines Board, the Netherlands

The European Medicines Agency (EMA) recently published a guideline regarding the involvement of pharmacogenetics (PGt) on the pharmacokinetic (PK) evaluation of drugs. It is the scope of this presentation to summarize the EMA guideline concerning PGt in early drug development.

It is generally acknowledged that the PK of virtually all medicinal products utilized in the human organism are prone to interindividual variability, which is due, to intrinsic and extrinsic factors, amongst which PGt. In recent years, a rapid development in our understanding of the influence of genes on interindividual differences in drug action has occurred. The exploitation of this knowledge allows for the improvement of the drug development process, and advances the accuracy and precision of drug action on their target. The latter, in turn, leads to less adverse drug reactions (ADRs) and increases the individualization of patient treatment.

Until now, translation of knowledge regarding the effect of genomic variations (both, metabolizing enzymes and drug transporters) into specific recommendations has been difficult, partly due to the limited attention often given to such genomic variations prior to registration. The aim of formally including PK-related PGt investigations in recommendations during the drug development process is to facilitate the evaluation, prior to registration, whether exposure to the active drug in genetic subpopulations differs from the general population so much as to necessitate a change in dosing, and warrants a specific recommendation.

It is appreciated that PGt might not be equally important for the development and clinical consequences of all drugs. However, the EMA guideline provides a framework as to where it is highly recommended or necessary to implement PGt in the drug development process.

The new EMA guideline, from a regulatory point of view, provides information on several critical issues related to the implementation of PGt into the PK-related evaluation of novel drugs. For instance, the situations and stage(s) throughout the clinical development program where PGt-related PK studies should be performed are described. Further stated are the regulatory considerations and/or requirements (e.g. related to study design, selection of subjects, and sampling) for PGt-related PK studies that investigate the effects of polymorphisms at the ADME level (enzymes, drug transporters, binding proteins and other relevant proteins). Information regarding when the clinical impact of genetic differences on PK parameters should be evaluated, as well as advice on the type of supporting studies that may be needed for posology and treatment recommendations for genetic subpopulations are provided. A discussion on possible consequences concerning genetically determined differences on PK parameters for treatment recommendations and labelling are also included. Finally, special considerations on the integration of drug-drug interactions (DDIs), as well as the effect of impaired or immature organ function in conjunction with PGt-related PK studies are given.

In the guideline, recommendations are made on how to implement PGt during the different phases of drug development, starting with the in vitro studies that are conducted before investigation in man (phase I throughout IV). Importantly, the guideline distinguishes between required and recommended procedures throughout the drug development process. The discrimination between these terms is based on cut-off values that define the 'important PK pathway' for decision-making purposes.

The Guideline is centred around the principle that the ultimate aim of phase II investigations with respect to PGt should be to optimize the posology and design of the phase III studies, including the decision of whether genotype-based dosing should be applied or not. Unless it is reliably shown that a difference in active substance and metabolite exposure has little consequence on efficacy and safety, the EMA expects genomic variations related to PK to be compensated with dose adjustments. This may be achieved either via genotype or phenotype based dosing or individual dose titration based on Therapeutic Drug Monitoring (TDM).

In all clinical phases of development, prospective banking of DNA for genotype analyses is highly recommended, even when there are no obvious indications of a relevant genetic influence on PK. These strong recommendations ensure that unknown genomic variations or pathways of importance can be retrospectively identified and their clinical effects tested with adequate power.

Overall, the new EMA guideline focusses on some of the PGt issues where solid knowledge acts as a good foundation for decision-making. It is emphasized that determining the in vivo consequence of a mutation or complex pattern of mutations and careful reasoning is always necessary to reasonably appreciate genomic variations for future drug development and dosing. This expectedly will lead to an ever increasing precision in patient treatment.

"Guideline on Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies + case-study"

By **Michael Pacanowski**, Food and Drug Administration, USA

Pharmacogenomic studies are increasingly being performed in drug development programs to characterize sources of variable pharmacokinetics or responses, and to develop companion biomarkers that guide drug use. Over the years, the U.S. FDA, EMA and other agencies have provided guidance to industry on data submissions, development of diagnostic tests, and the use biomarkers in specific

therapeutic areas. This presentation focused on recent FDA guidance regarding the generation of pharmacogenetic data in early phase trials and the potential implications for subsequent trials.

Session 2: Methodology and adaptive designs and in confirmatory clinical trials

Chairperson: **Robert Hemmings**, Medicines and Healthcare Products Regulatory Agency, UK

Co-chairperson: **Francesco Pignatti**, European Medicines Agency, UK

“Reflection paper on methodological issues associated with PG biomarkers for patients’ population selection”

By **Krishna Prasad**, Medicines and Healthcare Products Regulatory Agency, UK

The CHMP and European Medicines Agency (EMA) recently published a draft paper on certain methodological issues associated with evaluation of biomarkers and patient selection for clinical trials involving genomic biomarkers.

Biomarker research has been at the forefront of medicine for sometime and more recently there has been sudden upsurge in the interest in genomic markers with a view to make best use of the ability to identify and utilise individual variability in drug response. The exploitation of the ability to identify specific groups/ individuals who differ in the benefit they derive from treatment/drug due to a particular genetic characteristic or to avoid an adverse reaction is an attractive option. In order to achieve this, it is necessary to tailor clinical trials during drug development and other areas to maximise the output in terms of differentiating the effects in those with or without the markers. In this context, it is the predictive ability of the marker for drug response that is of greatest interest although; markers that have prognostic value are also of interest.

The paper detailed some of the experiences at the CHMP and the certain difficulties in designing clinical trials. The difficulties, whether real or perceived do present issues that should be considered before during and after the design of the trials. Some aspects of the trial design and the different options are discussed based on the regulatory experience so far.

Retrospective data analysis is an important aspect of biomarker development genomic or otherwise. It is possible that the marker may not be identified during early development or the value is not clear due to the relatively small population studied. With increasing population exposure later in development or in the post marketing phase, occasionally rare events/ risks become evident and there are genuine concerns of initiating a trial in such circumstances. The paper also discusses the limitations of retrospective datasets and some possible ways to overcome them.

The aim of the presentation is to highlight some of these issues and generate interest in the panel discussion. The panel discussion should also address some points that are of great interest but where available experience is limited.

“Adaptive designs”

By **Martin Posch**, University of Vienna, Austria

The knowledge on the genetic basis of many diseases is increasing rapidly and therapies are developed that target underlying molecular mechanisms. If, as a consequence, the benefit risk-balance of treatments varies across sub-populations defined by specific genetic features or other biomarkers, the population (which may be a subpopulation of biomarker positive patients) where a treatment has a positive benefit risk balance has to be identified. However, by enthusiastically over-interpreting large effect estimates observed in some genetic subgroups one may be misled by the (biased) data. From a statistical viewpoint this amounts to a subgroup analysis problem. It is well known that statistical testing for a positive treatment effect in multiple subgroups leads to a substantial inflation of statistical error rates unless an appropriate adjustment for multiplicity is performed.

Especially, if subgroups are defined by several biomarkers, the number of potential subgroups increases exponentially with the number of biomarkers considered. If the overall sample size is not increased accordingly, statistical tests have insufficient power due to low sample sizes per subgroup and the required multiplicity adjustment. An approach to increase the efficiency of such clinical trials are adaptive enrichment designs. They allow to start a trial with a broad population and to select a more promising (sub-)population at an adaptive interim analysis. In the second stage the trial is enriched by recruiting only patients of the identified (sub-)population. Thereby, with the same overall number of patients as in a fixed trial design, more subjects of promising sub-populations can be recruited. Furthermore, information of subjects in both parts of the trial are used in the appropriate adaptive statistical test procedures to increase the power of the trial. In the application of these designs in confirmatory clinical trials the potential gain in power needs to be weighed against the additional complexity in the planning, conduct and interpretation of such trials compared to simpler design options.

“Evaluation & implementation challenges with prognostic/predictive genomic signatures in clinical drug development”

By **Viswanath Devanarayan**, Abbott Laboratories, UK

Genomic and other biomarkers in clinical drug development have become increasingly important for a variety of purposes such as for predicting treatment efficacy and adverse events, identifying patients likely to progress in disease, dose selection, etc. Biomarker signatures are developed for these purposes during early research and later qualified to fit their intended use in clinical drug development. There are a number of practical considerations associated with the evaluation and implementation of these biomarker signatures, such as analytical and biological variability, biological relevance, assay availability, predictive performance evaluation, robustness, study design and translation. The importance of each of these considerations for successful execution of genomics and biomarker strategy in drug development will be illustrated via brief case studies in this presentation.

Session 3: Post-approval pharmacogenomics: impact on Risk Management Plans and Information

Chairperson: **Isabelle Moulon**, European Medicines Agency, UK

Co-chairperson: **Krishna Prasad**, Medicines and Healthcare Products Regulatory Agency, UK

“New Pharmacovigilance legislation and genomics”

By **Peter Arlett**, European Medicines Agency, UK

- Opportunities for public health and pharmacogenomics:
 - Need to strengthen the system
 - Objectives and measures in the new legislation
 - Implementation
 - impact
- Steps in the Pharmacovigilance process:
 - Risk management planning
 - Collect and manage data
 - Detect and manage signals
 - Evaluate safety issues
 - Benefit risk assessment
 - Regulatory action / risk minimisation
 - Communication
 - Audit
- Opportunities from the new Pharmacovigilance legislation:
 - Opportunities for improvement
 - 9-years in the making
 - Objectives and measures
 - impact
- New legislation impact:
 - Biggest change to the legal framework for human medicines since 1995
 - Entire product life-cycle impacted
 - Major change project that will take a few years to fully implement
 - Establishment of the PRAC is key milestone
 - Opportunity to better collect and better analyse PGM data for public health
 - Full implementation estimated to save between 500 and 5,000 lives per year

- Savings to society between 250 Million Euros and 2.5 Billion Euros per year

“Concept paper on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products”

By **Qun-Ying Yue**, Medical Products Agency, Sweden

There can be large variability in the response to drug therapy in terms of both efficacy and safety. Some of the variation is related to genomic variations. Consequently, there may be subsets of patients with a different benefit/risk profile.

At the time of marketing authorisation, information on the safety of a medicinal product (MP) may be relatively limited for genomic sub-populations. Rare but serious ADRs (e.g. skin or hepatic reactions) may be identified late in the drug development phase or post marketing.

Guidance is needed on the evaluation of pharmacogenomic specific issues in the conduct of pharmacovigilance in order to inform and improve clinical use of specific treatments.

The concept paper discusses e.g. the following: 1) how to give systematic consideration of the implications of genomic biomarker guided use of MPs in the risk management plan for concerns relating to lack of efficacy / effectiveness, or safety; 2) conditions when and how post-authorisation genomic data may need to be collected; 3) consideration of the level and type of evidence for identification/assessment of signals; 4) consideration of risk minimisation measures, depending upon the possible clinical implications (including provide information in the label).

Session 4: Pharmacogenomics guided treatments in clinical care: experience from patients and health care professionals (HCPs)

Chairperson: **David Haerry**, European Aids Treatment Group, Belgium

Co-chairperson: **Marisa Papaluca**, European Medicines Agency, UK

“Pharmacogenomics in HIV/HCV - Areas of urgent improvement”

By **David Haerry**, European Aids Treatment Group, Belgium

1. Positive examples

- Hypersensitivity abacavir – high predictive value, well accepted and established
- IL28B
 - For years, we have been wondering why some patients responded better to HCV treatment than others.
 - Finally, in 2009 three publications report that HCV patient with IL28B-CC genotype spontaneous clearance rates twice as high than IL28B-TT. The association is observed both in white and African Americans. Differences of genotype prevalence in both populations explain the different prognosis in these populations.
 - In addition, IL28B-CC patients SVR rates under therapy with Peg-Interferon-α and Ribavirin twice as high (C/C in African Americans 25%, Europeans 68%, East Asians 90%).

2. Neutral example

- Genetic factors influencing plasma concentrations in NNRTI: little impact on clinical practice; no explanation for hypersensitivity to nevirapine or CNS effects by efavirenz.

I have myself suffered of CNS effects and depression caused by efavirenz for years, and had troubles convincing my doctor switching to nevirapine, because he had lost a patient on this drug. However, for the 80% not affected by the hypersensitivity issue, nevirapine is a great drug with excellent long term safety and efficacy, neutral on lipids and great PK properties. The problem is really the management challenge in the clinic due to absence of a biomarker allowing to predict hypersensitivity.

3. Negative example

- Tropism testing pre CCR5 use:
 - Assay has become the cloven foot in CCR5 use.
 - First assay done by one lab in the US; blood samples had to be shipped on dry ice, waiting 6 weeks for the result.
 - Also, tropism poorly understood in the beginning (switch or expansion).
 - Difficult to approve better & more precise assays (drug label required use of trofile assay).
 - Assay reimbursement issues:
 - Switzerland no problem
 - Italy: MAH has to reimburse labs
 - Germany: Insurers won't pay, MAH is legally not allowed to pay
 - Spain: depends on hospitals being able to perform the tests
 - UK: MAH is reimbursing labs
 - Assay impacts label:
 - First line therapy naïve approved US 2009, Canada 2010, AUS 2012
 - EMA rejected 2009
 - CH: MA withdrew application Aug 2012
 - From a patient perspective, this is a drug that should be prescribed in first line. The price would have to go down of course. The reasons for this drug to be first line are evident: excellent safety, tolerability and efficacy in the long run, and higher prevalence of CCR5 tropic patients in naïve population.

Things we should improve on:

- Pharmacogenetic testing should be built in as option in pIII pivotal trials when specific side effects such as hepatotoxicity, rash or hypersensitivity reactions occur.
 - At this moment, industry is nervous when such things occur.
 - Drugs are killed and taken off the market if 5, 6 such events occur.
 - Are we overreacting? Most likely.

- We should do everything possible to allow such medicines be administered safely by immediately running pharmacogenetic studies immediately.
- Examples Nevirapine, recent issue with BMS HCV compound stopped in pIII after 9 hospitalisations and one death.
- There is concern among patients giving consent for potential pharmacogenetic studies to be run in the future. We need to inform patients better on why this is important, and we should be aware of issues related to data protection when shipping samples abroad.
- Interpretation pharmacogenetic testing
- Regulatory differences when better assays become available – should be avoided, patients and public don't understand this.
- Alemtuzumab
 - This drug has been SoC for patients with a genetic predisposition for chronic lymphatic leucemia.
 - Taken off the market because lower dose is useful in MS, the manufacturer Sanofi wanted to optimize its future profits.
 - Authorities approve withdrawal of MA – this is unethical.
 - This is a situation where industry is shooting in its own legs, and is even getting regulator approval for doing so.

Summary, dreaming a little (going back to HIV)

- We have gone very far, approving ca 30 compounds in 6 drug classes in the last twenty years.
- We accumulated a lot of know how about
 - Drug interactions
 - Resistance
 - Monitoring drug levels
 - Impact of kidney function at baseline
 - Checking MI risk via Framingham score, etc.
- What I would like to see is an application for a tablet or a smartphone, which would use all available data from the individual patient and guide prescription by the physician by showing a chart of all available drugs (red: avoid / yellow: ok to use / green: excellent to use).
- At this point, complex information has to be collected from different sources and websites, which is challenging for a decision making process where the prescriber is under time pressure or sometimes even has limited access to all available information.
- Payers and public health systems are often taking decisions which are uninformed or in contradictions to those taken by the regulator.
- We may need patients and clinicians at the table to make the required pressure for improving implementation of existing pharmacogenetic know how.

"Genomic Guided Therapy in Cancer Patients"

By **Robert Diasio**, Mayo Clinic Cancer Center, USA

The standard of care today for the treatment of most types of cancer in Europe and the United States continues to be based on traditional Phase I, II, and III clinical studies. This approach has utilized initially determination of doses of individual drugs or agents that have tolerable toxicity and anticancer efficacy, and then later comparative studies (of single agents or drug combinations) to establish prioritization of which drugs should be used first, second, and third line for each cancer type.

Over the past several decades, it has become increasingly clear that there is significant variability in the way that various patients respond to the same dose of a cancer chemotherapy agent, thought likely to be due to genetic differences. Mutations in genes coding for drug metabolizing enzymes were initially shown to be responsible for increased toxic reactions to cytotoxic chemotherapy agents, e.g., 6-mercaptopurine, Irinotecan and 5-Fluorouracil. Subsequently and more recently in particular with more targeted therapeutic agents, it has become apparent that mutations in genes controlling important steps or receptors important in drug activation determined whether a therapeutic agent would be effective, leading to the development of diagnostic tests that could predict whether a particular agent would likely be effective before the agent was administered, e.g. Cetuximab, Vemurafenib, and Crizotinib.

With the completion of initial sequencing of the human genome in 2000 and with more rapid and less expensive methods for sequencing resulting in the identification of an increasing number of "driver genes", it has become possible to ask the question whether a patient's tumor may be sampled before therapy to identify in amore general sense which agent or combination of agents is best to use for antitumor effect. Furthermore and potentially equally interesting is the potential to implant tumor specimens into immunologically compromised mouse "avatars" that in turn can be used to screen for potentially effective novel agents and/or combinations of agents even before some of these agents have entered the clinic.

While there are certainly no guarantees that the above approach will result in more effective treatment and prolongation of life, it does represent a new and perhaps more logical drug selection, although admittedly more expensive and still quite time consuming.

"Clinical implementation of pharmacogenetics: 7 years of experience"

By **Ronald van Schaik**, Erasmus Medical Center, the Netherlands

The amount of publications identifying potential clinically relevant pharmacogenetic markers is high (>1,000 articles/year) and is increasing exponentially. The quality of evidence is improving, as is the awareness about pharmacogenetics and its acceptance as a potential tool to improve healthcare. The number of laboratories performing pharmacogenetic tests are still low, but increasing, whereas costs for genotyping are decreasing. Therefore, pharmacogenetic testing may be a valuable tool to reduce adverse drug reactions and improve efficacy of drug treatment.

Thus far, clinical implementation of pharmacogenetic testing has been rather limited. Lack of education and awareness, lack of proof of clinical usefulness and negative cost-effectiveness studies have been put forward as inhibiting factors. Being genetic test, pharmacogenetic analysis seems to be treated different from other laboratory tests. But also much more trivial factors seem to be causing slow uptake. Our laboratory has offered pharmacogenetic testing for patient diagnostics since 2005, starting with 8 genes (TPMT, BChE, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A5 and DPYD). In 2012, our test menu also includes VKORC1, CYP1A2, CYP2B6, CYP3A4, SLCO1B1, HLA-B*5701, HLA-B*1502 and

HLA-A*3101. During our 7 years of experience, we have performed pharmacogenetic testing for 2,000 patients. Actions taken for successful implementation will be addressed, as will be unexpected difficulties encountered in a clinical setting.

Session 5: Pharmacogenomics guided treatments in clinical care: experience from patients and health care professionals (HCPs)

Chairperson: **Tomas Salmonson**, Medical Products Agency, Sweden

Co-chairperson: **Jane Moseley**, European Medicines Agency, UK

“IVDD revision”

By **Fabio Faraulo**, European Commission, Belgium

The existing regulatory framework for *in vitro* diagnostic medical devices ('IVD') has demonstrated its merits but has also come under criticism in recent years. In an internal market with 32 participating countries and subject to constant scientific and technological progress, certain divergences in the interpretation and application of the rules have emerged, thus undermining the main objectives of Directive 98/79/EC, i.e. the safety and performance of IVDs and their free movement. The revision aims to overcome these flaws and divergences and to further strengthen patient safety. The revised regulatory framework will be more robust and more transparent, while at the same time supportive of innovation and the competitiveness of the IVD industry. Key elements of the revision include a clarification of its scope, the inclusion of provisions concerning the designation and functioning of Notified Bodies, the identification and traceability of devices, the registration of devices and economic operators, the introduction of a risk-rule based classification system and the introduction of specific requirements for clinical evidence for IVDs.

“Companion diagnostics”

By **Stuart Hogarth**, King's College, UK

In this presentation Stuart Hogarth offered some reflections on the progress which has been made in developing a regulatory framework for pharmacogenomics over the last decade and discussed some of the key challenges which remain.

He highlighted some of the most significant achievements which have helped to lay the foundations for the routine application of pharmacogenomics in clinical practice: the creation of a pre-regulatory space for sharing data between industry and regulator; the creation of a pre-competitive space for industry/academic collaboration on the development of new tools and standards; and a commitment to international harmonisation amongst the three leading regulatory agencies. He highlighted the novelty of these developments but also discuss the ways in which they relate to broader trends in the regulation of pharmaceuticals.

He used the example of warfarin pharmacogenetics to explore some of the significant challenges which remain for the adoption of personalised medicine in the clinic. Underlying these challenges is the complexity of the governance framework for pharmacogenomics, in particular: firstly, the presence of multiple gatekeepers in the post-marketing regulatory space, with varying degrees of commitment to personalised/stratified medicine, and different approaches to the evaluation of healthcare interventions and secondly, the lack of alignment between the regulatory frameworks for pharmaceuticals and for

diagnostic devices. He concluded with some suggestions about how these challenges might be addressed.

"HTA of Companion diagnostics"

By **Elisabeth George**, National Institute for Health and Clinical Excellence, UK

New treatments that are recommended in NICE health technology appraisal guidance should be funded in the NHS if the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments. In addition, there are other forms of NICE guidance, for example for medical technology, interventional procedures, diagnostics and NICE clinical guidelines that help ensure that new treatments find their place in the health service. How companion diagnostics assessed by NICE depends on if the companion diagnostic is to be added to an established treatment pathway, or if the development of the companion diagnostic forms part of the development of a new drug. NICE has assessed a number of drugs that have been licensed for use in patient populations that need to be identified with companion diagnostics. Examples of these will be presented together with the challenges faced during the assessment such as post hoc subgroup analyses, data on comparators, the availability and accuracy of the diagnostic test, and the prevalence of the respective biomarker. NICE is currently developing guidance on a companion diagnostic as part of an established treatment pathway, and the difference of the two approaches will be discussed.

Session 6: Pharmacogenomics in the global landscape: Pharmacogenetics and Ethnicity

Chairperson: **Stephen Spielberg**, Food and Drug Administration, USA

Co-chairperson: **Emer Cooke**, European Medicines Agency, UK

"Genomics in Patients with Hispanic ancestry"

By **Adrian Llerena**, CICAB University hospital, Spain

The genetic polymorphism of the most studied cytochrome P450, CYP2D6, is among the major determinants of the interindividual and interethnic variability of pharmacokinetics and drug response. Two CYP2D6 phenotypes have been described: "poor metabolizers" (PM), and "extensive metabolizers" (EM) including a group of Ultra-rapid Metabolizers (UMs).

Pharmacogenetics of Hispanic populations. Hispanic populations are diverse according to their genetic composition resulting from the inter-ethnic crosses between Amerindians, Europeans and Africans. The frequency of PMs and UMs in Spain is 7-10% and 4.9%, respectively (Llerena et al., 2009). The RIBEF Network Project aimed to evaluate the most relevant CYPs genetic polymorphism in different Ibero-American populations (from Spain, South-, Central-Caribe and North-America. Differences have been found, the frequency of CYP2D6 PMs ranged from 6%-3.9% in Nicaraguans-Cuban-Mestizos.

CYP2D6, Antidepressants discontinuation and Suicide. A higher frequency of UMs has been found among individuals who committed suicide (Zackrisson et al, 2010). One explanation for this relationship could be treatment failure with antidepressant drugs metabolized by CYP2D6 (Llerena et al., 2004) widely used to prevent suicide or to treat mood disorders. A complementary explanation could be via the implication of the polymorphic CYP2D6 in the endogenous metabolism. CYP2D6 has been associated with behavioral and clinical risk factors such as personality and vulnerability to

psychopathology (Llerena et al., 1993; 2007; Gonzalez et al., 2008; Peñas-Lledó et al., 2009, 2010). Consistently, we found a relationship between UMs and severity of suicide and lifetime history of suicidal behavior among Eating Disordered patients (Peñas-Lledó et al., 2010, 2011, 2012a). Moreover it seems also been related to antidepressant discontinuation as recently shown (Peñas-Lledó et al 2012b).

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“Genomics in Patients with Japanese ancestry”

By **Yoshiaki Uyama**, Pharmaceuticals and Medical Devices Agency, Japan

It has been recognized that genomics has an important role to determine drug efficacy and safety. In recent years, number of drugs which require pre-genomic test to assure its benefit/ risk balance was increased. One of the points to consider in pharmacogenomics (PGx)-based drug development is similarities and differences on ethnic factors among populations. For example, a strong association of HLA-B*1502 with CBZ-induced SJS has been reported in Han-Chinese population, but not in Japanese population. Instead, HLA-A*3101 has been suggested as an important allele to predict the CBZ-induced cutaneous adverse drug reaction, including SJS, in Japanese and European populations. When conducting multi-regional clinical trials, effects of ethnic factors relating to PGx should be taken into consideration in planning a study and evaluating data. Accumulating PGx data in consideration of ethnic factors will facilitate an understanding of clinical impacts of PGx in each population. To further promote PGx-based drug development, more international harmonization is necessary and discussion with a regulatory agency from an early stage of drug developments is a key to success.

“Differences in strength of association across racial/ancestral groups”

By **Steven Lewitzky**, Novartis, Switzerland

The strength of an association between a genetic/genomic biomarker and a clinical outcome (response to drug, risk of an ADR, risk of a disease) may differ across racial groups. Thus, if the intended use of such a biomarker is to predict patient response to a drug or identify patients at elevated risk for an ADR, its ability to make accurate predictions may differ across racial groups. Unfortunately, without very large sample sizes drawn from each of several racial groups it is generally not possible to reliably quantify these differences, or to determine the factors responsible for any difference observed. And since clinical trials are typically comprised of patients predominantly from one or a small number of racial groups, large samples from several such groups are usually not available. As a result, biomarkers identified as predictors of clinical outcome may differ in their predictive ability across racial groups in ways we are unaware of and for reasons we do not understand. This raises several important questions regarding the approvability and labeling of drugs for which such biomarkers have been identified. Here we pose several such questions, focusing on biomarkers for elevated risk of ADRs as these may have stronger implications for drug approvability and labeling.

3. Biographies of the chairpersons and speakers

Falk Ehmann



Falk Ehmann, MD, PhD, MSc, is currently working in the Scientific Support and Project Section of the European Medicines Agency (EMA). His main responsibilities include holding the Scientific Secretariat of the Innovation Task Force promoting Innovation and new methodologies in drug development and being involved in the development of policies, guidelines and the annual working program in these areas. Areas of expertise include Pharmacogenomics, Nanomedicines and Borderline and Combined Medicinal Products (including Devices), and other -omics especially in connection with Personalised Medicine. He has special expertise in the development of Similar Biological Medicinal Products with focus on monoclonal antibodies and Vaccines. He held various positions and responsibilities at the EMA since 2004, including Scientific Advice during product development and working in the Oncology and Anti-Infectives therapeutic area of the EMA Unit for Human Medicines Development and Evaluation.

Prior to joining the EMA, Dr. Ehmann was a Public Health Researcher at the Robert Koch Institute in Berlin and Medical Intern at different University Hospitals including Bordeaux, Munich, Berlin, Geneva and Tanzania where he achieved his Master in Public and International Health. Falk Ehmann wrote his PhD thesis in the department for Cellular Signal Transduction at the University Hospital Hamburg-Eppendorf in the Centre of Experimental Medicine of the Institute of Biochemistry and Molecular Biology.

Marisa Papaluca



Internal Medicine specialists, Marisa Papaluca joined the European Medicines Agency (EMA) in London, UK in late 1994 and occupied scientific and managerial positions in the EMA Unit for Human Medicines Development and Evaluation. Deputy Head of Quality up to 2002 and of the Efficacy and Safety Sectors up to 2009, Marisa is currently Head of Section for Scientific Support and Projects providing scientific support to the Agency core activities in transversal and multidisciplinary areas such as clinical trials statistical methodology, raw data analysis, non-clinical drug development, pharmacogenomics and nanotechnology.

The Section is also in charge of the EMA Innovation Task Force, reference group at EU and international level for innovative pharmaceuticals developments with current increasing activities on novel clinical trials designs, genomic biomarkers, combined products, nanomedicines, and synthetic biology. The section also runs the Business Pipeline activities contributing to the Agency's preparedness toward the upcoming Marketing Authorisation submissions.

Agnes Saint Raymond



Agnes Saint Raymond obtained her MD from Lariboisiere-St Louis University. She qualified as a Paediatrician in 1987 and worked as Chef de Clinique in Paediatrics in Necker-Enfants-Malades Hospital (Paris) with special interest in paediatric gastro-enterology, rheumatology and cystic fibrosis. She spent five years in pharmaceutical companies, then joined in 1995 the French Medicines Agency as Head of a Pharmaco-Toxico-Clinical Assessment Unit. In 2000 she joined the European Medicines Agency (EMA) in London, EU, a decentralised Agency of the European Union, working with the network of national regulatory Agencies in Europe.

She is the Head of Sector for Special Areas (which includes Paediatric Medicines, Orphan Medicines, Scientific Advice, the Small & Medium-sized Enterprises Office, and Scientific Support & Projects) in the Unit for the Development and Evaluation of Human Medicines. She has been in charge of the implementation of the European Paediatric Regulation, a new legal framework of the European Union, which mandates development of medicines, including age-appropriate formulations, for children from birth to adulthood wherever there is benefit or unmet paediatric needs. She is also the Chair of the WHO network of Regulatory Agencies on Paediatric Medicines (PmRN).

Frédérique Nowak



After a master in bioengineering from the Ecole Centrale of Paris, France (1992), Frédérique Nowak started her career at the Institut Gustave Roussy in Villejuif, France, where she got a PhD in Molecular Pharmacology in 1996. After her PhD, she joined Genset, a biotechnology company, where she has been project manager for innovative projects in high-throughput molecular cytogenetics.

Between 2002 and 2006, she was responsible for a R&D team at the Serono Genetics Institute of the Serono pharmaceutical company in Evry, France. Frédérique Nowak is currently Head of the Department of Innovation at the Institut National du Cancer (French National Cancer Institute, INCa) that she joined in 2006.

Hans Georg-Eichler



Hans Georg-Eichler has been Professor of Clinical Pharmacology at the Medical University of Vienna, Austria, since 1992. In 2003, he assumed the position of Vice Rector for Research and International Relations at the same University. Professor Eichler holds an MD from the Vienna University Medical School, Austria, and a Master of Science in toxicology from the University of Surrey, Guildford, UK. He received his clinical training at the Vienna University Hospital and the Poison Control Centre, in Austria, as well as at Stanford University, USA. He gained experience in outcomes research most recently as a visiting professor of outcomes research at the world headquarters of Merck & Co. Prior to that, his research took him to several institutions in the USA, the UK and South Africa. Professor Eichler is a member of several medical advisory boards at the Austrian Ministry of Health. Since 2000, he has been President of the Vienna School of Clinical Research. Professor Eichler was a member of the Committee for Orphan Medicinal Products from April 2000 to June 2002, and has twice served as a member of the CHMP Scientific Advice Working Party.

Krishna Prasad

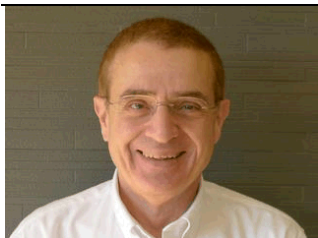


Currently, Krishna Prasad has a dual role at the MHRA, the UK regulatory Agency as an Assessor and Unit manager. He is also a practising cardiologist with a special interest in cardiovascular genetics and personalised medicine. He has been member of the Pharmacogenomics Working Party of CHMP since its formal inception. In addition, he is also a member of the Cardiovascular Working party of the CHMP/EMA and the Co-rapporteur (EU/CHMP representative) for the ICH process relating to the E-14 guidance document.

Prior to joining the MHRA, Krishna worked as a BHF supported Research Fellow and Lecturer in Cardiology. His special areas of interest are heart failure, arrhythmias and sudden death where he was involved in research as an academic, with a number of publications. Areas of special interest outside of cardiology are Pharmacogenetics/pharmacogenomics, stratified medicine and drug innovation and has

been author on abstracts, publications including peer review papers, book chapters and editorials. He has interest in development of regulatory guidance and in enhancing the interaction between academia, regulators and the other stakeholders.

Federico Goodsaid



Federico Goodsaid, Ph.D., is Vice President for Strategic Regulatory Intelligence at Vertex Pharmaceuticals. His work at Vertex is focused on early and effective interaction and collaborations on exploratory and product biomarkers with regulatory agencies. He was previously Associate Director for Operations in Genomics and Biomarker Qualification Coordinator at the Office of Clinical Pharmacology/Office of Translational Sciences/ Center for Drug Evaluation and Research/ U.S. FDA, working on the regulatory application and development of genomics and biomarkers at the FDA. His B.A. was in Biochemistry and Biophysics from the University of California at Berkeley and his Ph.D from Yale University in Molecular Biophysics and Biochemistry. He was a Postdoctoral Fellow at Cornell University and at Washington University in St. Louis. Before he joined the FDA, he was Senior Staff Scientist at Applied Biosystems and Lead for the Molecular Toxicology Group at the Schering-Plough Research Institute.

Marc Maliepaard



Marc Maliepaard, PhD, clinical pharmacologist, since 2001 appointed as senior clinical assessor and clinical pharmacologist at the Dutch regulatory agency CBG, with a focus on clinical pharmacokinetics and pharmacogenomics. He is a member of the Pharmacogenomics Working Party (PgWP) at EMA.

Marc received his PhD in 1994, on mechanistic research into the binding of mitomycin C analogues to DNA. Further post-doctoral research aimed at identification and characterisation of transport proteins and the consequences of modulation of such transporters on efficacy and safety of oncolytic drugs.

Michael Pacanowski



Dr. Pacanowski is a Clinical Pharmacologist and Team Leader of the Genomics Group in the Office of Clinical Pharmacology at the FDA. Dr. Pacanowski received his Pharm.D. from the Philadelphia College of Pharmacy. He then completed clinical training at Bassett Healthcare in Cooperstown, NY and a clinical research fellowship in Cardiovascular Pharmacogenomics at the University of Florida, where he also received his M.P.H. Dr. Pacanowski's expertise is in the area of genetic epidemiology and public health genomics, specifically as related to pharmacogenomic strategies in drug development and utilization. At the FDA, he oversees review of investigational and new drug applications, contributes to regulatory policy development, and conducts research that supports FDA's core public health mission.

Robert Hemmings



Rob Hemmings is a professionally qualified medical statistician. He has been with the Medicines and Healthcare products Regulatory Agency (previously Medicines Control Agency) for 11 years and heads the group of medical statisticians. Much of Rob's time is spent educating medical colleagues in the importance and artistry of clinical trial statistics; their use in proof and in obfuscation. Rob currently holds the following positions within the European drug regulatory system:

- CHMP member: CHMP is the body responsible for preparing the opinions of the European Medicines Agency on all questions concerning medicinal products for human use. Rob is one of the 32 voting members of this key European committee.
- Chair of the CHMP's Scientific Advice Working Party (SAWP) with responsibility for preparing advice to the pharmaceutical industry on the appropriate tests and trials to conduct in the development of a medicine for marketing authorisation. This group includes approximately 50 regulatory scientists from across the European regulatory network and handles approximately 400 scientific advice / protocol assistance and qualification of biomarker procedures each year.
- Rob is also a member of CHMP's Biostatistics working party with responsibility for giving advice on matters relating to clinical trial methodology across the EU regulatory network.

Rob regularly speaks at national and international scientific meetings on a broad range of topics relating to medical statistics and drug licensing.

Martin Posch



Martin Posch is professor of Medical Statistics at the Medical University of Vienna. Lastly, he worked as statistical expert at the European Medicines Agency (London, UK) in the Human Medicines Development and Evaluation sector, where he contributed to guideline development and the assessment of study designs. He has a PhD in Mathematics from the University of Vienna and was scientific assistant and associate professor at the Medical University of Vienna until January 2011. His research interests are group sequential trials, adaptive designs and multiple testing, focusing on applications in clinical trials and Bioinformatics. Martin Posch serves as Associate Editor of Biometrics and Biometrical Journal.

Viswanath Devanarayan



Dr. Devanarayan is the Global Head of Exploratory Statistics at Abbott, where his group supports drug discovery applications, pre-clinical studies and clinical biomarker research. He received his Ph.D. in Statistics from North Carolina State University in 1996. He has ~16 years of combined pharmaceutical research experience from Eli Lilly, Merck, and Abbott. As an active member of some professional associations, he has co-authored several white-papers with regulatory, academic and industry scientists and offered training courses on topics such as Immunogenicity, ligand binding assays, high throughput screening, genomics and biomarker validation. He is also an adjunct faculty at Northern Illinois University.

Isabelle Moulon



Isabelle Moulon is Head of Medical Information at the European Medicines Agency (EMA) in London, UK. She is a qualified medical doctor from the University of Grenoble, France. She is a specialist in endocrinology and metabolic diseases and has done Post-graduate studies in nutrition, statistics and methodology. Isabelle worked as a clinical endocrinologist in hospital until 1987 and then joined the Directorate of Pharmacy at the French Ministry of Health. She worked for the pharmaceutical industry from 1992 to 1995 before joining the European Medicines Agency (EMA) in July 1995. She was responsible for Scientific Advice until December 2000. She was appointed Head of Sector for Safety and Efficacy of Medicines in January 2001. Since September 2005, she has taken up new responsibilities as Head of Medical Information. She also chairs the Name Review Group (NRG) and co-chairs the EMA Patients' and Consumers' Working Party (PCWP).

Peter Arlett



Education:

- Degree in Medicine from University College London (UCL) (1991).
- Member of the Royal College of Physicians (MRCP) of London (2004).
- Member of the Faculty of Pharmaceutical Medicine (MFPM) of the Royal College of Physicians of London (2002).
- Fellow of the Faculty of Pharmaceutical Medicine (FFPM) of the Royal College of Physicians of London (2007).

Career to date:

- Head of Pharmacovigilance and Risk Management Sector, European Medicines Agency (2008-present)
- Principal Administrator, Pharmaceuticals Unit, DG Enterprise and Industry, European Commission (2003-2008).

- UK delegate to the European Committee for Human Medicinal Products (CHMP) (2001-2003).
- Specialist Assessor and Manager, Medicines Control Agency (now MHRA) (1996-2001).
- Hospital Physician, UK NHS, UCL, Oxford, Hammersmith (to 1996)

Qun-Ying Yue



Dr Yue is a clinical pharmacologist trained at Karolinska Institute, Sweden. She obtained a doctoral degree presenting studies on interindividual and interethnic differences in drug metabolism. Dr Yue joined the Swedish Medical Products Agency (MPA) in 1996. She had more than 15 years' experiences about pharmacovigilance and she is a Senior Expert at the MPA. Dr Yue is a member of the Pharmacovigilance Risk Assessment Committee (PRAC) and the Pharmacogenomics Working Party (PGWP) under the European Committee for Medicinal Products for Human Use (CHMP).

David Haerry



David Haerry is a treatment writer and conference reporter since 1996. Since 1998, he is co-authoring a database on travel & residency restrictions for people living with HIV (www.hivrestrictions.org).

He is working in HCP education projects as coordinator and trainer with the Clinic for Infectious Diseases and Hospital Hygiene at the University of Basel/Switzerland and as a management advisor for the European AIDS Clinical Society.

He is involved in a number of European and global research networks and research collaborations:

- Europrise (Network of Excellence in biomedical HIV prevention research and early product development), Steering Committee
- International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), Community Advisory Board

- European Network of Centres for Pharmacoepidemiology and Pharmacovigilance ENCePP, Steering Group
- Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium PROTECT-IMI, External Advisory Board
- Swiss HIV Cohort Study SHCS, Scientific Board
- ART Cohorts Collaboration, Steering Committee
- Collaboration of Observational HIV Epidemiological Research Europe COHERE, Steering Committee
- European Patients' Academy for Therapeutic Innovation EUPATI-IMI, WP Leader and Executive Committee member

He is a member of the Patient and Consumer Working Party at the European Medicines Agency since 2006 and has served the European AIDS Treatment Group EATG in various positions since 2004.

David has been involved in HIV drug development since 2005 and has specific interests in the areas of Personalised Medicine, Risk Communication, Pharmacovigilance, Observational Studies, Biomedical Prevention and HIV Eradication Research. He is living with HIV since 1986.

Robert Diasio



Robert B. Diasio, M.D. is Director of the Mayo Clinic Cancer Center, Professor of Pharmacology and Oncology and William J. and Charles H. Mayo Professor.

- National Cancer Institute (NCI) funding since 1978
- MERIT Awardee
- Member/Chair, 14 cancer center external advisory boards
- Member, Board of Directors, Association of American Cancer Institutes
- Member, Board of Scientific Advisors, NCI
- Co-chair, National Clinical Trials Network Working Group, NCI
- Principal Investigator, Mayo Clinic Cancer Center Grant
- Clinical interest: gastrointestinal oncology
- Basic research interest: pharmacogenomics and clinical pharmacology of anticancer agents
- >200 peer-reviewed publications

Ronald van Schaik



Ron van Schaik (PhD, Clinical Chemist, Associate Professor Pharmacogenetics) works at the Dept. Clinical Chemistry at the Erasmus University Medical Center Rotterdam. He leads the Pharmacogenetics Core Laboratory, the Research & Development section and Thorax Laboratory. He has a focus on Pharmacogenetics, both research and clinical implementation. Topics are: 1. Transplantation/immunosuppression (cyclosporin, tacrolimus, MMF); 2. Oncology (taxanes, tamoxifen), 3. Pain (morphine, tramadol, propofol); 4. Psychiatry (antidepressants, antipsychotics); 5. HIV (efavirenz, nevirapine) and 6. Anticoagulation (coumarins). He has published over 120 articles in the field of pharmacogenetics. Next to pharmacogenetics, his expertise includes cardiac markers (troponins) and prostate cancer biomarkers (PSA).

Dr van Schaik participates in international advisory committees on pharmacogenetics (a.o. IFCC Task Force Pharmacogenetics (Chair), IATDMCT Pharmacogenetics Committee (chair), Dutch Task Force Pharmacogenetics (chair), European Pharmacogenetics Research Network (Steering Committee), European Society for Personalized Medicine (treasurer), European Society for Pharmacogenetics and Theranostics (Chair Scientific & Clinical Implementation Division), Personalized Medicine Division AACC) and the Pharmacogenetics Working Group of the European Medicine Agency. In 2001, he received the Ortho Clinical Diagnostics Award for outstanding research, in 2009 the AACC Outstanding Speaker Award and in 2010 the AACC/Mol Pathology Poster Award for Outstanding Scientific Research. Since 2008, his Laboratory is internationally recognized as an IFCC Reference Laboratory for Pharmacogenetics.

Tomas Salmonson



Tomas Salmonson, M.Sc., PhD, brings outstanding experience and expertise from a long career in the regulation of medicines both on a national and European level to his new role. A pharmacist by training, he is currently senior scientific advisor at the Swedish Medical Products Agency (MPA) in Uppsala, Sweden. He has been a member of the CHMP for more than 12 years. Since 2007, Dr

Salmonson has been the elected vice-chair of the Committee. He has been acting chair of the CHMP since April 2012 and is also chair of the EMA Pharmacokinetics Working Party.

Fabio Faraulo



Fabio Faraulo works for the Health Technology and Cosmetics Unit of the Directorate General Health and Consumers of the European Commission. He is in charge of contributing to the strategies, concepts, procedures and policies in the framework of the implementation of the Directives on medical devices, with a particular focus on environment, traceability and borderline products issues.

Stuart Hogarth



Stuart Hogarth is a member of the Department of Social Science, Health and Medicine at King's College London. Stuart's work combines empirical research in a political sociology framework with normative analysis of public policy and commercial strategy. Stuart is interested in understanding how post-genomic science enters clinical practice as personalised medicine and his research maps and analyses the emergent socio-technical regime which supports that translational process. He has a longstanding interest in the regulatory framework for genomic diagnostics.

In recent years he has produced policy reports and briefings for Health Canada and the European Commission and the Human Genetics Commission (HGC) on the regulation of genomic diagnostics and on the impact of gene patenting on diagnostic innovation. Between 2005 and 2010 Stuart worked with the HGC on the issues surrounding the direct-to-consumer genetic testing sector, latterly as a member of the UK working group convened by the HGC which developed a Common Framework of Principles for the sector. His work on the regulation of genetic testing received a Leveraging / Collaboration Award from the US Food and Drug Administration and he participated in the drafting of the OECD's guidelines on quality assurance for molecular genetic testing. Stuart has been on the organising committees for international meetings on the regulation of genetic testing in the United States, Japan and Europe. He is continuing his work in this area as a member of the FP7 EuroGentest network with a particular focus on the proposed new EU regulation for IVD devices.

Elisabeth George



Elisabeth George has an MPhil in Biology and a PhD in Genetic Toxicology from the Free University of Berlin, and an MSc in Economic Evaluation in Healthcare from City University London. Elisabeth worked at the Federal Health Office in Berlin and in the pharmaceutical industry in the UK before joining the Technology Appraisal Programme at NICE in 2003. Elisabeth is responsible for the development of technology appraisal guidance from one of the Appraisal Committees, has piloted the Scientific Advice Programme and is also involved in NICE's contributions to EUnetHTA.

Stephen Spielberg



Stephen P. Spielberg is Deputy Commissioner for Medical Products and Tobacco of the U.S. Food and Drug Administration. A pediatrician and pharmacologist, Spielberg was most recently the Marion Merrell Dow Chair in Pediatric Pharmacogenomics, and Director of the Center for Personalized Medicine and Therapeutic Innovation at Children's Mercy Hospital in Kansas City. Previously, he served as Dean of Dartmouth Medical School and Vice President for Health Affairs at Dartmouth College in Hanover, NH. From 1997 to 2003, Dr. Spielberg was Johnson & Johnson's Vice President for Pediatric Drug Development and, prior to that, was Executive Director at Merck & Co.'s Research Laboratories. During that time, he was Chairman of the Pediatric Task Force of PhRMA, the drug industry's trade association. He received his bachelor's degree in biology from Princeton University, and an M.D. and Ph.D. (Pharmacology) from the University of Chicago.

Adrian Llerena

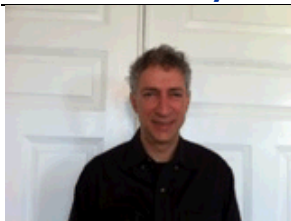


Since 1986, Adrian Llerena's research is focused on Pharmacogenetics and Clinical Pharmacology, specifically on Clinical Psychopharmacology. His PhD Thesis was the first pharmacogenetic study of Spanish population including psychiatric patients. Later, his research at Karolinska Institute was focused on Clinical Pharmacogenetics of antipsychotic and antidepressant drugs. During his stay at UCLA he was working in a NIH funded project about Pharmacogenetics of antidepressants in Mexican-Americans. Since 2006, I am the coordinator of the Iberoamerican Network of Pharmacogenetics (www.ribef.com) currently composed by more than 40 Latino American, Portuguese and Spanish Research Groups. His current position is Director of the Clinical Research Centre at Extremadura University Hospital (1000 beds) conducting Clinical Research, Clinical Trials and Clinical Pharmacogenetic Studies (www.cicab.es).

Yoshiaki Uyama



Yoshiaki Uyama is currently the leader for Omics Project in Pharmaceuticals & Medical Devices Agency (PMDA) of Japan. He is also Director, Review Planning Division, Office of Review Management, PMDA. He received his Ph.D. degree from the Nagoya City University in 1994 and became a research fellow for Japan society for the promotion of science. He was a post-doctoral fellow in University of Calgary, Canada in 1994-1995 before being a researcher in the Tokyo Metropolitan Institute of Medical Science (1995-1998). In 1998, he joined the Ministry of Health and Welfare (present: Ministry of Health, Labour & Welfare) as a technical officer. He started his review for new drugs in Pharmaceuticals & Medical Devices Evaluation Center of National Institute of Health Science (PMDEC) in 2001 and continues his career on drug review in PMDA since April 2004, including the career as the Director for regulatory science research (2010-2012), Review Director (2007-2010), ICH Technical Coordinator (2004-2009) and the topic leader of ICH E15 and E16.



Professional experience:

- Novartis Institutes for Biomedical Research, Cambridge, MA (USA)
Senior Principal Biostatistician, Department of Biomarker Development, 2004-present
- Millennium Pharmaceuticals, Cambridge, MA (USA)
Senior Biostatistician, Department of Clinical Development, 2003-2004
- Millennium Pharmaceuticals, Cambridge, MA (USA)
Biostatistician, Department of Human Genetics/Personalized Medicine, 1996-2003
- Data Resources Inc., Lexington, MA (USA)
Economist, Interindustry Modeling, 1983-1994

Education:

- University of Michigan, Ann Arbor, MI (USA)
Master of Science, Biostatistics, 1994-1996
- Brown University, Providence, RI (USA)
Bachelor of Science, Applied Mathematics/Economics, 1979-1983