Delegates were welcomed to the three-day Symposium by TOPRA’s Executive Director, Lynda Wight; Craig McCarthy, Chair of the Symposium Working Party and Helder Mota Filipe, Vice-President of the Executive Board of Infarmed, Portugal.

The keynote speech was given by André W Broekmans, BroekmansConsult, the Netherlands, on “Regulatory Affairs: Quo Vadis?” An experienced regulator looks to the future of the discipline – where is it going? The presentation examined the current and potential future regulatory system (with a focus on Europe) by discussing three broad themes: collaboration and globalisation; complexity; transparency. The collaboration between members of the European and wider regulatory community has enabled the creation of standards (such as ICH, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) which have allowed for common ground between different countries’ approaches to regulation of medical products and also inspections. In the future state there is a push to make the ICH guidelines more binding but also expand to current non-ICH countries.

New legislation (for example in medical devices and human pharmacovigilance) has imposed a greater burden on drug development companies but is also welcomed in areas where previous guidance was lacking (such as in the post-approval phase). It was questioned whether we had gone too far with excess committees in the European Medicines Agency (EMA) and the lack of freedom to manoeuvre within the complexity of these committee structures. In the future it was proposed that the focus would be more on regulatory science within initiatives such as the Innovative Medicines Initiative (IMI) to look at new viewpoints for the current regulatory system. Other future developments include the use of more progressive/adaptive licensing, post-approval changes and the alignment of regulatory review with health technology assessment (HTA) review – to eliminate the need for two separate systems each with their own unique complex processes. Finally, with respect to transparency, delegates were reminded that medicines have an inherent risk and that there is a need to educate the public. The contentious issues surrounding data-sharing are about the release of the decision-making data to the public (specifically the data around the benefit–risk decision) balanced against the need to protect subjects to avoid the misuse and misinterpretation of data. The European Federation of Pharmaceutical Industries and Associations (EFPIA) concept of responsible data-sharing was commended for its pragmatic approach focusing on accountability.
SESSION 1:
Clinical Trial Regulation Proposals
Reported by Sarah Roberts, Executive Director, Global Regulatory Affairs, PRA International, UK

Helder Mota Filipe, Vice-President of the Executive Board of Infarmed, chaired the session and opened with a presentation of how the new proposed Clinical Trials Regulation came about, and provided an update of the current status of the Regulation.

The Clinical Trials Directive (2001/20/EC) is widely acknowledged as one of the most contentious pieces of pharmaceutical legislation in recent years. Issues during the transposition of the directive resulted in a non-uniform approach across Europe. The proposed Regulation has been identified as the best solution to provide a uniform approach to the process. Over the past year, many issues have been discussed among the regulators and these discussions are still ongoing. Key topics that have arisen which have been identified by Infarmed include: timetables; Ethics Committee role/evaluation; compensation; and risk classification. The clear message was given that there will be no room for “national flavours” in the new regulation.

The first speaker, Ingrid Kössler, Member Group III, European Economic and Social Committee (EESC), EU, Sweden, provided an overview of the draft Clinical Trials Regulation. The presentation started with a reminder to the audience of the shortcomings of the current Clinical Trials Directive, 2001/20/EC. This was labelled “the most criticised piece of legislation across the entire EU pharmaceutical legislation range”, with the number of clinical trials decreasing, the cost of trials increasing (insurance costs up 800%, staff costs up by 107%) and increasing delays to initiating a clinical trial by 90% to an average of 152 days. It was interesting to note that the...
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number of clinical trials has also decreased in the US over the same timeframe, suggesting a continuing impact of the global economic crisis. However, it was recognised that despite these challenges, as a result of harmonisation between the Clinical Trials Directive 2001/20/EC and the Good Clinical Practice (GCP) Directive (2005/28/EC), clinical data generated anywhere in the EU are accepted as regarding subjects’ rights and safety as well as data robustness and reliability. The Proposed Clinical Trials Regulation allows for harmonised authorisation, a single portal for submission, flexible and swift assessment procedure and clear timelines with tacit approval. Since the European Commission’s draft Regulation was published in July 2012, the proposals have been reviewed by the European Economic and Social Committee (EESC) and a Member of the European Parliament (MEP), Glenis Willmott, resulting in various amendments and a report from the Environment, Public Health and Food Safety (ENVI) Committee in June this year, resulting in significant changes to the Commission’s proposal. Negotiations are still ongoing as there are still many minor obstacles, but acceptance of the new legislation should occur in 2014.

Susan Sandler, Senior Director, Regulatory Affairs (CRS), Parexel International Ltd, UK, provided an update on the industry viewpoint on the revision of the legislation on clinical trials. Overall, the Commission’s proposal was seen as an improvement on the Directive but in certain areas (data transparency, regulatory burden, reducing the costs of running a clinical study) it was felt that the proposed Regulation could have gone further. The main ethical principles for performing clinical research were discussed: autonomy/respect; benevolence/non-malevolence; and justice/universalism. The need for a harmonised regulation removing “national folklores”, and the future role and responsibilities of ethics committees, were discussed in the context of these ethical principles. In addition, there was further discussion around data transparency and the benefit for the whole scientific community for the provision to publish clinical trial data. There was also a call for the new EU database of clinical trials to be accessible to patients throughout Europe in their own languages for greater transparency and to enable more access to clinical trials.

SESSION 2:
New EU Medical Device Legislation, Borderline Products, HMA and CAMD Cooperation
Reported by Carla Gomes, Global Regulatory Affairs Leader, PPD (Pharmaceutical Products Development), Portugal

Margareth Jorvid, CEO, Regulatory Affairs & Quality Assurance, Methra Uppsala AB/Senior Partner, LSM Group, Sweden, introduced the speakers and explained that the session would cover the revision, current status and upcoming changes of the EU Medical Devices Directives, as well as addressing the classification of borderline products. Finally, it would discuss the recent initiatives to establish cooperation between the Heads of Medicines Agencies (HMA) and the Competent Authorities for Medical Devices (CAMD).

Erik Hansson, Deputy Head of Unit, European Commission, Health and Consumers Directorate General, focused on the new regulations and other changes to the medical device legislative framework in the EU, emphasising the theme of constant change. A review of the legislation was provided, specifically mentioning the three directives that were implemented into national legislation based on common EU regulatory principles, leading to the concept of the “new approach”. This is a very important concept as it differs considerably from what regulatory professionals are used to. Although the manufacturer is not obliged to prepare a submission package to submit and request approval to an authority, this approach encompasses obligations for manufacturers, notified bodies and competent authorities. This new approach relates to technical medical device products and is a flexible legislation that defines the essential requirements that are standard for the manufacturers to follow before marketing the devices. Ultimately,
these products will be CE marked. These requirements are under revision and will inevitability change given the many countries in the EU, and the risk of more divergence between countries.

An EU "Joint Plan for Immediate Action“ has been drawn up with the objective of strengthening the application of the existing legislation. This plan describes rules for the notified bodies (clarification of requirements, unannounced audits, re-assessment of bodies dealing with high-risk devices, joint audits of bodies by several member states and the Commission); for post-market safety and surveillance (member states reinforcement, Commission analysis and benchmarking, feedback on incidents to notified bodies); and for coordination and transparency (coordinated inspections, trend analysis and reporting, coordination with international partners, reporting by users and traceability).

Mr Hansson presented the “Regulation on the designation and the supervision by member states of notified bodies (Commission Implementing Regulation (EU) No 920/2013)”. This mentions the criteria for designation and surveillance, the joint audits, transparency and cooperation, the interpretation of designation criteria, the application form, the “Recommendation on a common framework for a unique device identification system of medical devices (Commission Recommendation No (2013/172/EU)) and the "Recommendation on the audits and assessments performed by notified bodies in the field of medical devices, (Commission No 2013/473/EU)”. The latter states the general guidelines, product and Quality system assessments and unannounced audits, and was adopted in September with immediate application.

Mr Hansson concluded with the information that the Joint Plan intends to strengthen the oversight of notified bodies, reinforce post-marketing safety, define the legal form, scope (aesthetic devices, genetic tests, etc), and risk classification. This topic was discussed as part of the European Parliament plenary vote on 22 October 2013, and the goal is to reach agreement in December 2013.

Sónia Cardoso, Health Products Directorate, Infarmed, Portugal, then presented on “Borderline products: How do we decide if a product is a drug or device?” A definition of a drug versus a medical device was provided. A drug is any substance or combination of substances which will function by exerting a pharmacological, immunological or metabolic action. A device doesn't achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its intended function (for diagnosis, prevention, monitoring, treatment or alleviation of disease, or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process or control of conception).

Nevertheless, the classification exercise for some products is still problematic. In fact, the Demarcation Principle states that, if after a case-by-case assessment, and taking into consideration all the characteristics of a product, the product falls within the definition of both medicinal product and medical device, then the Medicinal Product Directive (MPD) will apply. The Medical Devices Directive (MDD) states that in deciding whether a product falls under the MPD or the MDD, particular account must be taken of the principal mode of action. This may be deduced from the scientific data regarding mechanism of action and the manufacturer’s claims. Obviously, it is not possible to qualify a product in contradiction to current scientific data, and the manufacturer may be required to justify scientifically its rationale for the qualification of a product.

In order to discuss borderline and classifications issues, the Borderline and Classification Medical Devices Expert Group (MDEG-BC) has been created. This group aims to provide a forum to exchange opinions and reach consensus, so as to ensure a uniform approach to qualification of products and classification of devices.

Finally, to overcome regulatory flaws and gaps, and to further strengthen patient safety, the regulatory framework for medical devices has been revised. This revision has brought proposals in terms of the extension of the scope (products manufactured using non-viable human tissues or cells, or implantable/other invasive products without medical purpose similar to devices), as well as defined a clear exclusion of the scope (products that contain or consist of viable biological substances or organisms or food covered by Regulation 178/2002).

The concept and processes of HMA–CAMD cooperation were then explained by Reinhard Berger, Institute of Inspections, Medical Devices & Haemovigilance, BASG (Bundesamt für Sicherheit im Gesundheitswesen) and AGES (Austrian Medicines and Medical Device Agency). The CAMD is the medical device regulatory framework and the HMA is the medicinal product regulatory framework. While both classes of products are distinct and the regulatory frameworks are different, both are regulated as healthcare products and, as such, the assessment of safety and performance is the final goal.

Combining efforts into a joint cooperation seems intuitive. First, public expectation regarding safety, performance and other considerations such as suitability (including usability, affordability and availability) of healthcare products increases continuously. Secondly, regulatory systems are under increased scrutiny and pressure to become more effective and efficient, although in fact regulatory processes for both medicines and devices are continually being developed.
Regarding medical devices, the pre-market process, especially for high-risk devices such as implants, is under specific review. For medicinal products, the processes need to be updated on an ongoing basis in terms of pharmacovigilance, clinical trials and falsified medicines (and the related guidelines are continually being updated). Lastly, the new Clinical Trial Regulation is near final agreement (this Regulation will be aligned where possible with medical device clinical text).

Meanwhile, combination products are increasingly entering the market; companion diagnostic products and corresponding medicinal products resulting in personalised medicines are becoming more widespread, and it is possible to find convergence of products and different technologies in both markets. Issues and challenges exist for both categories: market surveillance, post-market surveillance including vigilance, and available resources to fulfil obligations and harmonisation between authorities.

Considering all of the above, it is judicious for the HMA and CAMD to join forces. The CAMD role includes the revision of legislation, implementation of the joint plan on medical devices (including joint assessments of notified bodies), reinforcing market surveillance and coordination, communication and transparency. Meanwhile, the HMA role includes the revision of legislation on pharmacovigilance, falsified medicines, clinical trials, veterinary medicines, and strategic review of structures.

The process of cooperation began with workshops in March 2011, leading to a HMA–CAMD formal session in January 2013. The key considerations presented in the context of this cooperation were: understand and retain relevant specificities of distinct regulatory frameworks, partnership and cooperation, appropriate representation and participation of all partners, ensure appropriate forums for technical, operational and strategic discussions and decision-making, more diverse membership and expertise and careful consideration of meeting burden and costs. The immediate benefits were to allow for discussion on topics of common interest (combination products, companion diagnostics, clinical research, optimising regulatory systems, exchange of information and identification of new issues/future areas, increased understanding and partnership). In addition, it will facilitate exchanges of experiences and best practices, cooperation and work-sharing, and promote benchmarking, peer review, training and mentoring, as well as applying a consistent approach to implementation of legislation.

The session chair, Maria Morais, Adviser of the Executive Board of Infarmed, Portugal, described the session objective as being an introduction to Infarmed, as well as information on the impact of regulatory and scientific activities on the medicinal product lifecycle.

The first speaker, Marta Marcelino, Head of the Pre-Marketing Authorization Unit, Medicines Evaluation Department, Infarmed, described the evolution of Infarmed as a reference member state (RMS) and the steps taken to reinforce this role and increase participation in the European system. The strategy, which began in 2008, saw a rise in Infarmed’s ranking among agencies from 14th in 2007 to 3rd in 2012.

With an increase in member states available to act as RMS from 2008, and an improved capacity through “slot booking”, parallel assessments were reduced as RMS assessments became more trusted, and in 2009 the national requirements for initial marketing authorisation applications (MAAs) were withdrawn.

The role as concerned member state (CMS) was reinforced by a strategic decision to strengthen international capacity, increase Infarmed’s participation at European and international levels, foster competitiveness in scientific assessments in the EU and further adapt the agency’s services to innovation and market needs.

In parallel, the HMA strategy paper for 2011–2015 led to further improvement in the operational efficiency of medicines authorisation through the decentralised and mutual recognition procedures (DCPs/ MRPs). These improvements include:

- Identifying with stakeholders’ which areas to address, and more targeted communication
- Risk-based proportionate regulation
- Harmonisation of assessment
- Worksharing
- Harmonised training to help achieve high-quality performance
- Ensuring interoperability of national IT systems within the European network, creating a competitive, boundary-free regulatory environment
- Dialogue with industry on operational matters, including through streamlining validation procedures.

Infarmed plans to actively participate in CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) activities in the HMA task force on resources and the CMDh Process Improvement Working Party. The agency will also continue to develop and monitor the timelines for validation of MAAs, timelines for “clock stop” periods for DCPs and the national phase timelines to grant marketing authorisations (MAAs).

Dinah Duarte, Head of Scientific Evaluation Unit, Directorate for the Evaluation of Medicinal Products, Infarmed, and Portuguese alternate member of CHMP (Committee for Medicinal Products for Human Use), spoke on the “Portuguese Experience at CHMP”. She covered areas of Portuguese intervention, mainly in the scientific assessment of the centralised procedure (CP) and representation on the CHMP working parties. She noted that a Portuguese CHMP member is the representative of the CHMP in the Healthcare Professionals Working Party and that Infarmed has two experts in the Scientific Advice Working Party at the EMA.
Since 1995, Infarmed has appointed nine CHMP members who have been responsible for the scientific evaluation and coordination of the scientific resources available within the national competent authority (NCA). Currently, more than 20 dedicated assessors are involved in the CP assessment teams and have gained experience in the review of dossiers and the preparation and provision of assessment reports for central or national MAAs in the relevant scientific areas.

To date, the Portuguese CHMP members have been involved in the evaluation of 117 CPs (either as rapporteur or co-rapporteur), 75 of which have been authorised. The main therapeutic areas evaluated by Portuguese teams in the past 18 years have been neurologic medicines (antiparkinsonians and antipsychotics), anti-infectives and antineoplastic medicines. During this period, the Portuguese CHMP members and teams were nominated to be rapporteur or co-rapporteur three to four times per year.

Alexandra Pego, Head of the Directorate of Risk Management for Medicines, Infarmed, gave an overview of the Portuguese pharmacovigilance system, its organisational structure, competences and main objectives, as well as participation in the harmonisation and standardisation of technical measures for pharmacovigilance, coordinated by the EMA. The speaker then described the adverse drug reaction (ADR) portal, created in July 2012 for online reporting of ADRs by healthcare professionals and consumers/patients. Statistics were given for paper versus online reporting, type of notifier and geographic distribution during its first year of implementation, with the following conclusions drawn: the majority of physicians report on paper, while pharmacists and patients are more likely to report online.

Emilia Alves, Adviser of the Executive Board of Infarmed, Project Coordinator, gave a presentation on the Portuguese project for codification of medical devices. This was developed to allow the Portuguese healthcare system to easily access medical device information: for the identification of all medical devices, their characteristics and purposes; for the manufacturers and distributors for an accurate evaluation and selection of medical devices; and to evaluate National Health Service (NHS) resources assigned to medical devices.

The foundation of the system is the existence of clear rules to register and update data on medical devices and market operators, and the definition that each medical device should have as a unique identification. The system comprises a data repository nomenclature to integrate all medical devices, where these devices are identified by a code, among other functionalities. Thus far, a legal framework requiring the use of the code to acquire and prescribe medical devices belonging to groups has been set up; some types of medical devices have already been codified and information collated on the quantities, value and costs of the devices bought by the Portuguese NHS hospitals; and real time information about the available medical devices in the market is obtainable, particularly their respective manufacturers and distributors.

Maria João Portela, Head of the Official Medicines Control Laboratory, Infarmed, gave an overview of Portuguese market surveillance of medicines, the official batch release of blood products and the analytical strategy against falsified medicines.

Infarmed’s laboratory analyses more than 1,000 medicines, from MRP/DCP products and CP products and also blood products, 20 active pharmaceutical ingredients (APIs) and 250 healthcare products (cosmetics and medical devices).
Infarmed is the official control authority batch release for blood products (OCABR), and analyses medicines suspected of being falsified. In European market surveillance, the Portuguese Official Medicines Control Laboratory (OMCL) is one of the most active participants, with four analysis projects per year in the EMA/EDQM CP testing programme, out of a total of 45-50 yearly in this programme for the EU. The OMCL has specific expertise in monoclonal antibodies, interferon and blood cell proliferation and differentiation factors (e.g., G-CSF).

Regarding falsified medicines, Infarmed cooperates in activities with other authorities, namely Customs, Police, and the National Authority for Economic Activities and Food Security (ASAE), as well as with African Portuguese-speaking countries.

The final session speaker, Nuno Oliveira, Coordinator, Research and Project Office, Infarmed, Portugal, briefly described market monitoring: numbers and trends, ongoing policy measures and the impact studies performed.

The presentation included statistics for the Portuguese market in terms of ambulatory and hospital markets, and highlighted the impact assessment studies behind some of the policies currently implemented or due for implementation in the future.

PARALLEL SESSIONS:
There were two parallel sessions led by Infarmed, the first on the Common European Submission Platform (CESP) and the second on variations.

Rui Vilar, MRP/DCP Product Manager, Marketing Authorisation Unit of Medicines Evaluation Department, Infarmed, described the use of CESP within the framework of the development of electronic submissions to Infarmed, and described the national requirements and the current and future use of CESP within the agency.

The recent history of switching from paper to electronic submissions was addressed. The business background in which the use of CESP began was presented in light of the current practical use of CESP within the agency, and how the combination of future use of CESP with regulatory/technological developments could support fully paperless submissions.

Gilda Calado, MRP/DCP Product Manager, Post Marketing Authorization Unit of Medicines Evaluation Department, Infarmed, then discussed the submission of variations, presenting the steps taken for implementation of Regulation EC No 1234/2008 (as amended by Regulation EU No 712/2012) to the national procedure on 4 August 2013. She highlighted activities such as:
- The update of the national portal for electronic submission of variations, allowing for exclusively online submission of all types of variations (IA/IB/I/grouping/worksharing) through national procedures and MRPs/DCPs, and also integrating payment of applicable fees
- Communication with applicants and training of staff at the agency, regarding the new requirements for exclusively electronic submission and handling of variations in accordance with the new regulation.

The presentation also included a discussion on processing variations, focusing on aspects such as validation, applicable timetables and finalisation of procedures in accordance with the Regulation.

Finally, Infarmed shared its view on how this implementation has impacted the activities of the agency, especially when dealing with the Regulation’s challenges and opportunities.

SESSION 4:
HTA and Reimbursement: A New Regulatory Initiative?
Reported by Louise Moore, Medical Writer and Regulatory Affairs Manager, Clinical Network Service (Pty) Ltd, Australia

The symposium’s working party chair, Craig McCarthy, Managing Director, CAMPHARM, France, introduced this session. The session considered how to best integrate health technology assessment (HTA) and reimbursement strategy into the drug development plan by exploring the common ground between regulatory and health economics and outcomes research (HEOR) departments; looking at how HTA bodies are jointly developing their strategies to harmonise their approach for providing advice; and by investigating the experiences from joint scientific advice with HTA bodies and regulators and how the regulatory affairs professional can be influential in good outcomes of these meetings.

The first speaker, Stefan Holmstrom, Director HEOR, Astellas, the Netherlands, discussed “EU HTA and Reimbursement Strategies for a Pharmaceutical Company: A Masterclass”. A changing healthcare environment has led to a number of factors having an increasing influence on healthcare decision-making, resulting in pressure and focus on healthcare budgets. These include advances in medical technology, an increasingly ageing population resulting in a rise in chronic illness, an increase in public expectation, an increase in the number and type of healthcare professionals, cost containment measures by payers (HTA, national or regional decision-making bodies), and slower economic growth. We need to understand how health systems work, what are the drivers of investment in healthcare, and acknowledge that these may differ depending on the setting. Emerging countries are likely to invest or increase investment in healthcare, although the US is still the single biggest market, and China is growing at speed.

After safety, quality and efficacy, HTA and reimbursement is often referred to as the fourth regulatory hurdle. HTA is a multidisciplinary process that summarises the information about the medical, social, economic and ethical issues related to the use of a drug, and aims to inform the formulation of safe, effective health policies that are patient-focused and seek to achieve best value. HTA acts as a bridge
between evidence and policy-making, and seeks to provide health policy-makers with accessible, usable evidence-based information to guide their decisions about the appropriate use of technology and the efficient allocation of resources. HTA looks at the clinical effectiveness and safety (how the health outcomes of the technology compare with available treatment alternatives such as standard of care), along with the cost effectiveness of the new treatment.

HTA is not new. The Australian Pharmaceutical Benefits Advisory Committee (PBAC) was established in the 1950s. Now there are a number of HTA agencies across Europe, including some regional as well as national agencies, and their level of involvement varies from country to country. Most national HTA bodies serve either in an advisory, regulatory or coordination role.

Mr Holmstrom continued by discussing the integration of HTA and market access needs in pharmaceutical development. A country-specific submission dossier (also called a value dossier) is required which will include a burden of disease overview, a clinical overview and an economic overview. This should focus on patient-relevant benefits (mortality, morbidity and safety), long-term data, comparative data and added benefit data. Effectiveness and efficiency need to be proven.

HEOR should be considered in the early stages of product development when the target product profile is first prepared, and work should continue throughout clinical development. More than 50% of the value dossier should be completed at the time of regulatory submission. Some points to consider during clinical development include the type of trial (in order to achieve a premium price, it is necessary to have evidence supported by a superiority rather than inferiority trial), whether it is possible to expand the inclusion criteria to reflect the general population, and what data can be obtained in pre/post approval studies to strengthen a company’s market access position.

The key recommendations from Mr Holmstrom were to tailor the global market access strategy based on product qualities, to be proactive, to ensure global alignment with development team members, to ensure the value dossier is available at marketing authorisation application/new drug application (MAA/NDA) approval, and to enhance skills and capacity internally to understand client needs.

Mira Pavlovic, Deputy Director for HTA, HAS (Haute Autorité de santé), France, then spoke on two topics: “The Coming Together of HTAs and Regulators for Good Advice for Quick Patient Access to Vital New Medicines – Myth or Reality”, and “Reflections on EU Regulatory Agency/HTA Joint Advice Meetings – Room for Improvement?”

Dr Pavlovic opened by discussing the mandate for EU collaboration on HTA, referring to the Article 15 Directive on the application of patients’ rights in cross-border healthcare and the Pharma Forum Recommendations. The EU will support cooperation and exchange of scientific information among member states within a voluntary network connecting HTA bodies, in order to reduce duplication of assessments by developing common assessment pre-reports and a template for the dossier in all EU countries. Early dialogue should also be considered during product development to improve the quality of the dossier.

The EUnetHTA is a voluntary network of HTA bodies in Europe, and is the basis for a permanent HTA network whose first meeting took place in October 2013. The specific actions of the EUnetHTA, coordinated by the HAS, France, are to improve the quality and appropriateness of the data produced by the introduction of early dialogue (scientific advice), disease-specific guidelines, additional evidence generation, general methodology guidelines, and a manufacturer’s template for submission. A recent initiative, supported by the European Commission, was the introduction of multi-HTA early dialogue on product development. Two preparatory pilots were completed mid-2012 in which nine agencies participated, resulting in a draft procedure.

In the multi-HTA early dialogue process, one indication is considered per procedure. The process is similar to the scientific advice procedure, with the EMA requiring the submission of a briefing document including questions, and resulting in a face-to-face meeting with the company and HTA organisations from which detailed minutes are validated by all HTA participants. Eight pilots have been completed in which the EMA was invited as an observer, and a survey of this process is ongoing.

Moving forward, the European Commission has now put out a call for tenders to facilitate the continuation of this process, which is aimed at products in Phase II and Phase III of clinical development. This aims to conduct ten early dialogue pilots (seven drugs and three medical devices, diagnostics or procedures) with at least ten HTA organisations to be included. All early dialogue meetings will be held in 2014, and this process will be free of charge to companies participating at this stage. The goal is to achieve a model for a permanent network. The whole process is coordinated by the HAS, France.

The logical next step would be moving towards parallel EMA and EUnetHTA advice, but we will have to await the results of the European Commission’s call for tender with integrating input from all interested parties.

**SESSION 5:**
**ICH: Where Are We Now? – Harmonisation through Globalisation by Convergence**

*Reported by Clare Lavery, Director, Global Regulatory Policy & Intelligence, Janssen Research & Development, UK*

In this session the evolution of ICH from its inception to the present day was provided, including a review of specific ICH achievements and their impact on the drug development process. The session, chaired by Dr Beatriz Silva Lima, University of Lisbon, Portugal, also explored the potential future direction of the ICH organisation, including plans for globalisation beyond the original three founding institutions.
regions of the EU, the US and Japan. The rationale for the recent changes to the ICH guideline development process, notably brought about to reduce industry influence, was also discussed.

Andre W Broekmans, BroekmansConsult, the Netherlands, gave the first presentation, entitled “An Overview of ICH: Organisation, Achievements and Guideline Process”. So far ICH output has included 20 quality-related guidelines, 14 guidelines on safety and 21 guidelines on efficacy, as well as the Common Technical Document (CTD), the Medical Dictionary for Regulatory Activities (MedDRA) and the Electronic Standards for the Transfer of Regulatory Information (ESTRI). Of these, Dr Broekmans highlighted some of the key impacts, such as: the ICH Q7 Guideline on Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients, which has since been upgraded as a World Health Organisation (WHO) document; the ICH Quality by Design (QbD) Guidance Documents (Q8, Q9 and Q10) that have introduced a paradigm shift in drug development; and, the ICH E6 Guidance on GCP that has led to greater acceptance of clinical data from those regions that have adopted this standard.

Dr Broekmans described the changes to the ICH procedures that were brought into effect this year as an attempt to better delineate the roles of industry and regulatory parties in the ICH process. The changes include the creation of the new role of regulatory chair, which supports the regulatory rapporteur by providing regulatory oversight of the guideline development process and by ensuring that the project timelines are met. Step 2 of the guideline development process has been revised and now consists of Step 2a, during which consensus on the technical document is reached by the six “core” parties, and Step 2b during which the draft guideline is adopted by the regulator parties. Another new element is that industry cannot now block the development of a guidance document.

Dr Lima then provided a review of the safety guidelines developed through ICH and their impact on the drug development process. The rapid increase in laws and guidelines on safety testing in the 1960s and 1970s that were prompted by a number of well documented disasters ultimately led to divergent technical requirements and duplication of tests internationally, which the ICH programme has sought to address. In this regard, ICH has had a huge impact on international drug development through the harmonisation of preclinical requirements, testing strategies and interpretations, creation of the harmonised CTD format, the reduction of animals in preclinical testing and the facilitation of dialogue among regulators worldwide.

Ongoing ICH procedures in the field of preclinical safety testing include the development of guideline M7 on the control of DNA-reactive impurities in pharmaceuticals and guideline S10 on photosafety testing. Another major development is the issuance of a regulatory notice concerning the revision of the S1 guideline on rodent carcinogenicity testing. The objective is to examine whether, for small molecule drugs, it is possible to anticipate the outcome of rodent carcinogenicity testing so as to avoid the need to conduct a long-term study.

Looking ahead to the future of toxicology testing in general, Dr Lima stated that greater use of multidisciplinary expertise will be required and that some of the current approaches may well have to be revisited. Aims will be to achieve better science through the use of less resource, so that the rate of drug development is increased, and to explore the potential for an animal-free preclinical programme, for example by use of human stem cells.

In the final presentation in this session Lenita Lindström-Gommers, Senior Policy Officer, European Commission Health and Consumers Directorate-General, Unit D5 – Medicinal Products – Authorisations, EMA, provided the views of the European Commission on the ongoing reform of ICH and the potential future of the ICH organisation. The Commission considers the ultimate responsibility for the ICH process to be that of the regulators who, in view of increased public scrutiny, must be seen to be acting independently from industry. With regard to increased transparency there are plans to publish more information on the ICH website in future, including the agendas and minutes of the Steering Committee meetings and the work plans of the expert working groups.

International outreach is another of the Commission’s goals for reform of ICH. Although there is agreement in principle that ICH should not be opened up to countries or regions that are not members of ICH, discussions on how to better involve these regions and on their membership criteria are ongoing. Other developments include the identification of new topics, which is on the agenda for the Osaka meeting in November 2013, and the potential for ICH to be established as a legal entity. The funding structure is also being examined with a view to developing a financing model that is more equitable and less dependent on the innovative industry.

SESSION 6: Combination Products – Clinical Development and Companion Diagnostics

Reported by Paolo Biffignandi, Director, VI.REL Pharma Sas, Italy; QPPV, EU Vigilance Ltd, UK; Senior Scientific Consultant, ELC Group, UK & CZ.

This session covered the challenges with clinical development for combination products and the impact of new legislation proposals. Swati Bhat, Clinical Assessor, MHRA, discussed how to create a successful clinical development plan for these products from the MHRA’s point of view. Starting from the definition of a medicinal product for human use and from the medical device definition, he pointed out that the crucial difference is the ability to cause a pharmacological, immunological or metabolic action, or the absence of this ability. However, when a medical device incorporates – as an integral part – a substance which, when used separately, may...
be considered a medicinal product and which is liable to act on the body with an ancillary action to that of the device (ancillary medicinal substance), that device must be assessed and authorised in compliance with the MPD. Dr Bhat gave several examples of drug-device combinations, where the medicine must have an ancillary function to be considered a device (for example, catheters/stents/grafts coated with heparin) or where the medicinal product is incorporated into a delivery device (eg, prefilled syringes). Thus, the primary intended purpose is what really matters, and this guides the decision for borderline products (eg, if the principal action is physical, then the product is a medical device). In this regard, pre-submission meetings to discuss classification, permitted claims and supporting data, are highly advisable.

Robert Geertsma, Co-Chair, EC Working Group on New and Emerging Technologies (NET WG), and National Institute for Public Health and the Environment (RIVM), the Netherlands, offered insight into converging technologies in Europe which lead to the crossing of borders between traditional categories of medical products such as medical devices, pharmaceutical products or human tissues. This combination of different technologies now includes nanotechnologies, cognitive and biological sciences, materials science and information technology. The process shows a high degree of innovation; however, it also brings new risks, such as an indisputably increased complexity, a language problem because of the many stakeholders, and the lack of specific training of clinicians and of regulatory professionals. The EC NET WG, founded in 2005, aims to ensure regulators are kept abreast of innovations, proactively considering whether the regulatory framework is appropriate to deal with new developments which usually require a multidisciplinary approach. Where challenges are identified, the WG will make recommendations to the Medical Devices Expert Group (MDEG) on the best ways of addressing them by, for example, formal regulatory change or the production of guidance. The WG comprises the European Commission (DG SANCO), member states, notified bodies and industry associations, and special interests groups in various disciplines, with the help of external experts.

Finally, David Jefferys, Senior Vice President for Global Regulatory Affairs and European Government/Corporate Relations, Eisai, UK, gave an industry perspective on the EU Commission proposal to regulate companion diagnostics (proposed In Vitro Diagnostics (IVD) Regulation No 2012/0267). He highlighted the need to make regulations “future-proof”. One of the main features is that, for companion diagnostics intended to be used to assess patient eligibility for a treatment with a specific medicinal product, the notified body shall consult before issuing an EU design-examination certificate. Additionally, on the basis of the draft summary of safety and performance and the draft instructions for use, an Agency or the EMA (through the accredited “Assessment Committee for Medical Devices”), should be consulted regarding the suitability of the device in relation to the medicinal product concerned. The opinion of these authorities will be included in the documentation of the notified body concerning the device. The same mechanism applies for changes affecting the suitability of the device in relation to the concerned medicinal product. Therefore, a regulator from the device and medicines sector will share responsibilities and knowledge. The timeline for a co-decision process of this proposal is not clear at the moment, and the European Parliament elections in June 2014 will likely have a critical impact, with possible delays.
To import active substances into the EU from July 2013 onwards, the conditions for non-listed third countries have been defined as follows:

- A “Written Confirmation” is required from the non-listed third country’s health authority on equivalence of GMPs and oversight
- A waiver (“Waiver 1”) can be sought, so that the imported API can be brought into the EU without restriction
- A waiver (“Waiver 2”) can be sought for exceptional circumstances, eg, to maintain a supply of medicines a member state may waive the requirement for a written confirmation.

Avoiding medicines shortages will require the cooperation of third countries (countries seeking listings and those providing written confirmations), the collaboration of stakeholders (with dialogue and information-sharing, and a willingness to seek pragmatic solutions to put the patient first) and industry engagement (with communication/ awareness initiatives by trade associations, qualification of new suppliers or site changes, collaboration with API suppliers to secure written confirmations and contingency planning to avoid supply disruptions).

In terms of API importation, issues still remain regarding atypical actives; equivalence assessment for “listing”; written confirmations (which can contain errors, or be of questionable validity); the renewal of written confirmations (with validity periods of between one and three years, depending on the country), the application of “Waiver 2” for importation; and finally on when the Falsified Medicines Directive (FMD) will be implemented into national laws in individual countries.

Another challenge relates to the registration of the API. According to the FMD, it should be registered by the competent authority of the member state and it defines the required dossier, procedure and deadline. But the deadline for registering activities was March 2013 and only three countries had issued guidance before this date.

Finally, more challenges were presented regarding the Good Distribution Practice (GDP) legislation for APIs and GMPs for excipients, which must be similar to GDPs for medicinal products and consistent with ICH Q7. But the major challenge with the FMD is still outstanding, ie, rules relating to a product’s “safety features”. It is expected that implementation of these features will take place between 2017 and 2023.

To summarise, it is crucial to understand the global supply chains and be aware of the risks. There is no need to wait for final implementing guidance of the FMD and its continuing efforts to address diversion, cargo theft, substandard medicines, counterfeiting, etc. There have been no shortages of medicines resulting from the FMD’s API importation requirements, due to tremendous efforts by all stakeholders to ensure patients are not affected.

Jim Thomson, Chair, European Alliance for Access to Safe Medicines (EAASM), UK, presented: "Welcome to the 21st century – threats and opportunities for patient safety”. EAASM is an independent, pan-European initiative. Its key activities include campaigning for the safer use of unlicensed or off-label medicines and the exclusion of counterfeit and substandard medicines from the supply chain; raising public awareness around such issues; and promoting effective legislation and enforcement in relation to falsified medicines. Counterfeiters infiltrate the legitimate medicines supply chain and also use unlicensed pharmacy websites to conceal their fake drugs among legal medicines. The EAASM decided to go directly to the target public who use these sites. The Alliance did this by creating a site similar to those selling falsified medicines, with a warning message for consumers who clicked to buy any of the advertised medicines. However, there are still too many misinformed patients with easy access to websites that promote counterfeit drugs.

Gerald W Heddell, Director of Inspection Enforcement & Standards Division, Medicines and Healthcare products Regulatory Agency (MHRA), UK, spoke on “Experiences of implementing the new regulation in reducing falsified medicines in the EU”. He began by giving an example of a counterfeit Heparin episode which resulted in the deaths of a mother and daughter, and the lessons learned from this. He noted that it is crucial for companies to check the security of their supply chains and to have adequate risk assessment and management systems in place. Patients need to have confidence in medical products, particularly pharmacy prescriptions, and recalls of counterfeit drugs undermine that trust. Mr Heddell provided information on the list of written confirmations already issued, the list of third countries (Waiver 1) and information related to the inspections by EU NCAs (Waiver 2).

Mr Heddell discussed the need for a single official logo for genuine internet sales, to be displayed on all relevant webpages, and he noted that the Commission is still working on this logo. Finally he mentioned that the upcoming rules on safety features will enable wholesale distributors and pharmacists to verify the authenticity of medicinal products, identify individual packs and determine if the outer packaging has been tampered with. In conclusion, the EU guideline on falsified medicines is still an ongoing process but we do have additional protection from falsified medicines; the supply shortages have been averted; the white listing is continuing on course; but there is confidence of written confirmations needs to be developed. The remaining key decisions for 2014 are on security features/tracking and the internet logo, and moving towards equivalence of global active substances.
The eighth session, chaired by Célia Alves, Director of Information and Communication Management, Informed, explored the use of social media by industry, regulators and patients. Paul Woods, Director, Paul Woods Compliance Ltd, UK, opened with an overview of the use of social media by industry and the need to comply with certain regulations and codes. There is a complex “jigsaw” of global, European and national laws which can be diverse and it is important to consider the implications across different jurisdictions, as social media communications easily cross national boundaries. Advertising unlicensed products is prohibited, but the definition of advertising is poorly set out and is open to different interpretations across Europe. The European Commission proposal on “Information to Patients” attempted to harmonise national interpretations but was highly controversial and not supported by EU member states. Mr Woods presented some examples of communications and whether they could be considered as advertising, and highlighted some guiding compliance principles from the UK’s pharma industry association, the ABPI’s Code of Practice Digital Communications Guidance. For example, recipients of “pushed” information must have agreed to receive it, and a medical information response to an individual is not considered as advertising unless it is made public, for example as an FAQ on a website. Twitter is probably not feasible for communication of prescription medical product information as, for example, communications can be re-tweeted. Company-run discussion forums or blogs must be moderated so content complies with the Code, and it was noted that this can become extremely resource-intensive. Companies need clear digital and social media policies that are communicated to employees.

In the second presentation, Martin Harvey Allchurch, Head of Communications, European Medicines Agency (EMA), described how the EMA is using social media in its communication strategy to its stakeholders. The online presence is a key element of the communications strategy with currently 250,000 people visiting the EMA website each month, often many times over. Used correctly, social media demonstrates openness and, most importantly, underlines the transparency credentials of regulators and the website. There is a huge demand for online healthcare information and regulators have a duty to improve access to validated reliable information. For the moment the EMA is taking a cautious approach but new EMA websites will integrate blogs and social media. The main social media channel at the moment is Twitter, where the focus is on news and events; others include LinkedIn for recruitment and news, and YouTube for events, workshops, training and information. Other national regulatory agencies are also engaging with social media, for example with different Twitter feeds for different topics.

Also highlighted was the new pharmacovigilance obligation in Good Pharmacovigilance Practice (GVP) Module VI (July 2012) for MAHs to screen internet and digital media under their responsibility for potential reports of suspected adverse reactions. This obligation recognises the rise in public sharing of medical experiences on social media. The Web Adverse Events (WEBAE) Project included in the IMI’s 9th call will research policy and technology solutions such as reporting “apps” and exploitation of social media sites to monitor pharmacovigilance. The EMA is well placed to facilitate coordination across different stakeholders in the consortium network and ensure that the project remains focused on public health. The conclusion was that social media is the new reality and regulators need to engage in the conversation. But be cautious as it cannot be controlled and you need to monitor and watch out for the unexpected.

In the third talk of this session Joseph Lama, Senior Information Systems Manager, Amgen, and on behalf of the European Patients’ Academy on Therapeutic Innovation (EUPATI), looked at the patient’s journey through a disease and how social media can empower patients to meet their needs. Patients’ needs include provision of accurate online health information, the ability to connect with healthcare professionals and other patients, to find providers of quality medicines, support from people such as caregivers and how to participate in research and clinical trials. Two examples of organisations addressing patient needs through social media were examined. The first example was RareConnect, which empowers patients with rare diseases to connect across the world, share experiences and obtain support from each other. From the website, patients can learn about research and the latest treatments and see what advocacy organisations are doing around the world. Currently there are about 40,000 visitors a month to the website and 45 patient communities from more than 30 countries.

The second example given was the European Patients’ Academy on Therapeutic Innovation (EUPATI), whose objective is to provide reliable, accurate and comprehensive information to patients on research and development of medicines. It aims to increase the capabilities of patients and patient organisations to be effective as advocates and advisors in research, clinical trials, with regulators and in ethics committees. EUPATI has a five-year programme to develop social media platforms to develop and disseminate information, and provide training on research
and development. Three platforms will be created: the “Training Programme”, which will use face-to-face learning and e-learning to train around 100 patient advocates, the “Educational Toolbox” using presentations and webinars to train 12,000 patient advocates, and the “Internet Library” using Wiki, YouTube and other social media internet sources to reach a broader section of 100,000 individuals.

The session concluded that there are excellent opportunities in the use of social media but there are also challenges and risks. Stakeholders must use tools that are compliant, transparent and open to scrutiny.

SESSION 9:
Generics: Small Molecule Pharmaceuticals and Large Molecule Biosimilars
Reported by Paolo Biffignandi, Director, VI.REL Pharma Sas, Italy; QPPV, EU Vigilance Ltd, UK; Senior Scientific Consultant, ELC Group, UK & CZ

This session was opened by Ana Cristina Vieira, Regulatory Affairs Director, Teva, Portugal, whose presentation was centred on the regulatory strategy for generics. Data exclusivity (and its exceptions for orphan designated drugs, paediatric medicines and significant new indications) and market exclusivity were discussed, as their interplay is a key step in the generic strategy. Four pillars were identified to maximise success: the choice of the procedure, the reference product, the legal basis, and the RMS. Although the centralised procedure (CP), mandatory for biosimilars and optional for generics of CP-approved products, was recognised to have fast and predictable timelines with a lower administrative burden and cost compared with the DCP, this latter is still used in the vast majority of generic applications, with the Netherlands being the most active RMS.

The state-of-the-art development of biologic medicines and biosimilars was discussed by João Gonçalves, Associate Professor, Faculty of Pharmacy, University of Lisbon, Portugal. Biologics have revolutionised modern medicine, since they offer real hope for many unmet medical needs and contribute significantly to improved survival rates, enhanced lifespan and a better quality of life. Estimates foresee that, by 2016, ten of the top 20 medicinal products will be biological (compare with six out of 20 in 2012) with patent cliffs around this year. For biosimilars, differences still exist between the approaches of the EMA and the US FDA. One of the major issues for these products is that their manufacturers do not have access to the details of the innovator process and so they are forced to become semi-innovators themselves. The science behind these products was Prof Gonçalves’ major theme, and he provided the audience with a thorough oversight on how a full scientific knowledge is key to minimise uncertainty and maximise success. This is especially true in the quality domain, where an extensive characterisation of the molecule and a comparison to the reference product may allow for an abbreviated preclinical and clinical development pathway.

Rosário Lobato, Associate Professor, Faculty of Pharmacy, University of Lisbon, Portugal, then debated the myths and the realities of generics in the EU. Quality issues have often been raised against generic medicines, but the EU legislation seems able to guarantee that their manufacturing process reflects the state of the art, thus allowing claims of essential similarity and interchangeability. Several other negative myths were presented, included the perception that results obtained in healthy volunteers in bioequivalence studies cannot be applicable to patients or special populations – a criticism clearly unfounded, since the goal of a bioequivalence study is simply to demonstrate formulation equivalence in promoting absorption and differences are usually much less than 10%. This general lack of confidence, as well as national prescription habits, may hamper the use of generic medicines. On the contrary, Prof Lobato concluded that the rationalisation of social resources with lower costs for conventional therapies could allow the allocation of more financial resources for innovative and more expensive therapies.

Along the same lines, Nuno Lages de Oliveira, Coordinator, Research and Project Office, Infarmed, Portugal, explained the policy measures to promote the Portuguese generics market. A fast-track in the reimbursement process analysis of generic medicines was adopted in 2013. Within its mission boundaries, Infarmed’s Office of Research and Projects has been actively exploring the creation of new draft proposals/measures to promote generic drug use and generic share growth. These draft measures are aimed at influencing the promotion of generics consumption within the entire drug supply chain, from the pharmaceutical industry to the prescribing physicians, pharmacies and patients.