

The 4th EMEA/TOPRA meeting on medicines legislation 2009:

Evolution to the next step – the needs of the future

1–2 December 2009, London, UK

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Keywords

Pharma Package; Pharmacovigilance; Risk management; EMEA/EMA restructuring; Heads of Medicines Agencies; Paediatric investigation plans (PIPs); Clinical studies; Variation regulation; CHMP

This joint TOPRA/European Medicines Agency (EMA) meeting raised the question: 'What will the future bring, and what do we need to know today?' Speakers discussed key events planned for 2010 and beyond.

SESSION 1:

European Union: The latest information on future regulatory activity for pharmaceuticals

Reported by Jenine Willis, Director of Editorial Services, TOPRA

Thomas Lönngren, Executive Director, European Medicines Agency (EMA), opened the conference by reflecting on the EMA's work in the 15 years since its launch. The Agency and the pharma industry have seen many changes over this period, perhaps the chief one being the increase in globalisation and its impact on drug development and manufacture. Like the US FDA, the EMA has 'had to go global' to find ways of ensuring the safety of medicines produced beyond their borders. Scientific developments, economic issues and the need for greater transparency are all shaping the future of drug regulation. Health Technology Assessments are becoming more important and will have an impact on the regulatory process. Emphasising the importance of dialogue, Mr Lönngren asked for feedback on the EMA's strategic '2015 Road Map'.

Irene Sacristan Sanchez, Deputy Head of Unit – Pharmaceuticals, European Commission Enterprise and Industry, gave an update on the progress of the Pharmaceutical Package. She noted that the Lisbon Treaty has now come into effect and this will have some impact on the unit's work and the Pharma Package. There are two elements to the Package. First is the Commission Communication, which is essentially a political declaration on proposals to meet the challenges facing the industry, including promoting innovation, access to medicines, globalisation and scientific developments. The second comprises legal proposals in three areas:

- Counterfeit medicines
- Pharmacovigilance
- Information to patients.

Regarding anti-counterfeiting measures, there are three key items under discussion to minimise the risk to public health. They centre on implementing a harmonised approach to track products, tighter control of the supply chain and a focus on ensuring good manufacturing practice (GMP) in active substances wherever they are produced, eg, through inspections. Much progress has been made during the discussions, and differences of opinion between member states on the details, eg, on safety features and active substances, have become clearer. This legislation is now at first reading stage in the European Parliament and should go to a vote some time in the Spring.

Pharmacovigilance (PV) has been hotly debated over the years and the existing framework has been revisited with a view to creating a more harmonised approach. The main issue has been clarity in ensuring clear tasks and responsibilities for all parties. A new, smaller EMA PV committee has been proposed that comprises experts rather than member state representatives. The idea is to streamline the process and ensure there is a single assessment of safety issues and that regulatory follow-up is harmonised. A major change in emphasis is in proportionality, ie, focusing on risk areas rather than treating all products as if they have the same risk.

The PV proposals are also still being discussed by the Council and are also at first reading stage in the European Parliament. Contentious issues to date for member states are the composition of the new PV committee and direct reporting to EudraVigilance.

Finally, although technically at the same stage as the other two pieces of legislation, the proposal on information to patients is proving more controversial. The Council has reacted very negatively to proposals that aim to develop rules that allow a workable distinction between advertising to patients and providing information for them. Despite this, the proposals are also due to undergo a first reading in the European Parliament in the Spring.

Noël Wathion, who heads the EMA Patient Health Protection Unit, presented the first draft of the Agency's Road Map to 2015. This document was due to be discussed by the Management Board the following week before going to public consultation. Mr Wathion noted that this document is a vision and not an implementation plan, as the latter will be down to the 'From Vision to Reality' document. The vision builds on the Road Map 2010 and sets out how the EMA can further develop as a public health agency.

Following a comprehensive review of the drivers for progress and change, the Agency evaluated its progress against the 2010 Road Map. It concluded good progress has been made, but that further work is still needed. Therefore the first priority for the next five years will be to further improve the delivery and quality of the Agency's core business. Three 'new' strategic areas were identified:

- Addressing public health needs – eg, identifying gaps in medicine development and providing incentives for unmet medical needs, and learning from outcomes of public health threats
- Facilitating access to medicines – eg, focus on improving and streamlining the medicines development process and improving benefit–risk analysis, as well as look at improving relative effectiveness assessments
- Optimising the use of medicines – eg, better post-authorisation follow-up.

The final presentation of Session 1 also focused on strategy. This time it was the Heads of Medicines Agency Strategy Paper II which was outlined by **Dr Marcus Mullner, Division Manager, Austrian Medicines and Medical Devices Agency**. The HMA vision, he said, is to protect public health and its mission is to foster an effective and efficient network. The HMA is a voluntary cooperative network which includes representatives from 27 member states plus three EEA countries and covers 44 national competent authorities.

Dr Mullner stressed that they were at the beginning of the process, and the recent first meeting had reviewed what had been achieved under the first strategy paper. Although much had been achieved, there is still a lot of ongoing work to do, he emphasised. Among the proposals for the next strategy document are assessing the HMA's vision and mission and promoting it better, including a review of the website. Other proposals include better training for national competent authority staff and improving benchmarking to establish best practices.

The proposed strategy is due to be discussed at various meetings during 2010 and it is expected that the final strategy should be adopted in Q4.

SESSION 2: Pharmacovigilance and risk management

Reported by Carolyn Hynes, Director, Global Regulatory Affairs Strategic Policy & Support, Johnson & Johnson Pharmaceuticals Group

This session, chaired by **Peter Arlett, European Medicines Agency**, and **Craig McCarthy, CAMPHARM**, covered new regulatory developments within the area of PV and the implementation in Europe of the ICH E2F Drug Safety Update Reports (DSUR) guideline.

Dr Arlett emphasised the EMA's position as the hub of the European Network for PV and the key function that EudraVigilance – the data processing network providing a common EU PV database accessible to all member states – performs in supporting EU PV and risk management activities. Operational since December 2001, a recent validation study (submitted for publication in the *Drug Safety* journal) provides direct evidence that more than 40% of safety issues can be detected earlier if EudraVigilance is used in addition to other PV resources.

The status of several EMA-led PV projects was noted, including ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance), a project to bring together experts in PV and pharmacoepidemiology in Europe in a Network of Excellence, and PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium), a collaborative European project aiming to develop innovative methods in pharmacoepidemiology and PV, which is funded by the Innovative Medicines Initiative (IMI) Joint Undertaking. The H1N1 influenza

pandemic is the current 'hot topic' for the PV function at the EMA. Monitoring the benefit–risk of the vaccines is ongoing, and the publication of regular EMA pandemic PV reports has been initiated.

An update on the status of the ICH E2F guideline, which aims to harmonise EU and US clinical trial periodic safety reporting requirements (without impacting on underlying legislation), was provided by **Barry Arnold, AstraZeneca**. The guideline is close to reaching Step 4 (guideline agreement) and implementation can be expected in 2010/2011. An annual evaluation of relevant safety information, the DSUR will have a different content and format compared with established reports. It should be concise and comprehensive, and focus on identifying and analysing potential risks. Importantly, the report, which has an extensive table of contents, will require cross-functional support to produce – in other words it should not just be seen as a 'safety document'.

Risk management and PV was the subject of the last presentation by **Stella Blackburn, EMA**. Establishing the safety specification – what is known and what is not known about a drug – is fundamental to a good risk management plan. Safety concerns can then be mitigated by PV activities and, if necessary, additional risk minimisation activities (detailed in a risk minimisation plan, RMP). In practice, implementing RMPs across the different EU member states is challenging because of diversity in medical practices, languages etc. Moreover, there are currently more than 50 products with additional risk minimisation activities, which can be complex and resource-intensive for healthcare professionals. An update to the current guideline on risk management systems (2005) is in progress, and a new draft can be expected early in 2010.

SESSION 3: Working internationally

Reported by Jenine Willis, Director of Publishing Services, TOPRA

Recent initiatives to promote international working, bilateral agreements and transatlantic cooperation were covered in this session. First onto the rostrum was **Emer Cooke**, the EMA's newly appointed **International Liaison Officer**, who gave an overview of the Agency's international strategy.

There is already a strong history of working together and this experience proved particularly useful in 2009, as the world tackled the swine flu pandemic. Cooperation is high on the EMA's agenda, and its long-term international vision includes creating synergies with international regulatory partners to minimise duplication of activities. The EMA is committed to strengthening its collaboration with the US (FDA), Japan (MHLW/PMDA) and Canada (HPFB). These countries have already implemented confidentiality and mutual recognition agreements with the EU. In particular, confidentiality agreements have been extremely successful and have enabled another recent development – the introduction of staff liaison placements during 2009.

While the EMA and FDA are most advanced in terms of cooperation, eg, sharing regular exchanges of information on applications, GCP inspections and public health areas or 'clusters', there are moves to extend this level of cooperation.

Fergus Sweeney, Head of Inspections Sector, European Medicines Agency looked at GCP inspections. With a significant number of pivotal trials taking place outside North America and the EU, regulators were increasingly relying on someone else's oversight systems.

It is not feasible to inspect all sites, so regulators need to be assured that systems are in place to protect subjects. Between 1 May 2004 and

1 August 2009, 1,397 GCP inspections were recorded on the EudraCT database, of which an increasing number are taking place in sites outside Europe and North America.

The EMA published a strategy paper on trials conducted in third countries in December 2008. This initiative set up a working party to develop practical approaches to protect clinical trial subjects.

Sweeney highlighted the positive role of joint working, as the EMA/FDA GCP inspection initiative has meant that regulators can share planning information as well as findings. Such activities will help meet the goals of promoting patients' safety wherever a trial takes place.

Continuing with the joint inspection theme, **Oliver Gross, Scientific Administrator, European Medicines Agency**, outlined some recent GMP joint inspection initiatives that the Agency has undertaken with other regulators.

The first project is part of the Transatlantic Administrative Simplification initiative, a framework for advancing economic integration between the EU and US. The objectives were to maintain or increase levels of public health protection through harmonising practices, reducing administrative burden and saving resources. As a result the EMA and FDA are piloting joint inspections of companies manufacturing pharmaceuticals in both regions. The programme is looking for volunteer companies to participate in the joint inspection pilot and would-be candidates could go to the EMA website at <http://tiny.cc/mPa5y>. Another project is the International API Inspection Pilot Programme, started in 2007 and based on the common GMP standard ICH Q7. To date, the work has increased transparency and visibility of inspections. It has helped reduce the number of duplicate inspections of the same product or sites carried out by more than one authority within a similar time period.

SESSION 4: Reacting and planning for change – EMEA/EMA restructuring

Reported by Vera Franzén, Regulatory Affairs Director, SentoClone AB, Sweden

The speakers for this session were **Patrick Le Courtois, Head of Human Medicines Development and Evaluation, EMA**, and two heads of national agencies, **Gro Ramsten Wesenberg, Norwegian Medicines Agency** and **Martina Cvelbar, Slovenian Medicines Agency**.

Dr Le Courtois described the reorganisation of the Agency that was about to be officially launched with focus on human medicinal products. The drivers for change were presented with respect to governance and management and the importance of preparing for future trends.

One of the main changes in the organisation is the introduction of a fourth level of management; section heads with full managerial responsibilities. No additional units have been created and focus is on processes and procedures.

Great emphasis is being placed on continuity; the Rapporteur and Safety and Efficacy Project Manager should be the same from pre-submission to post-authorisation, which is a new concept.

Dr Wesenberg gave a presentation on the HMA/EMA training strategy and its practical implementation.

Dr Wesenberg noted that there is an array of training available but a lack of coordination.

Joint training with industry would be possible but would not be easy for all national competent authorities (NCAs). The network should set the agenda, and confidentiality must be respected. It is

especially important for new members of the NCAs to understand the needs of industry and vice versa.

The creation of an EU office for regulatory training is proposed by the strategy group. It is believed that a physical office would be advantageous.

In the third presentation of this session, Dr Martina Cvelbar talked about availability of resources at NCAs for mutual recognition procedures (MRP) and decentralised procedures (DCP). An HMA/CMD(h) task force was set up in 2008 to deal with the problems caused by limited resources for MRPs and DCPs. A number of proposals have been made to improve the situation and, since January 2009, a uniform request form has been required to request a reference member state (RMS). This form is used by 20 of the 21 NCAs. More member states have started to act as RMSs but still more resources will be needed. Another problem is the duration of clock stops in DCP. It is suggested that 3 + 3 months would be a good rule and that clock stops beyond that would be possible only if agreed by all CMSs. Parallel assessment by CMSs should be avoided. The conclusion is that the work of the task force is progressing well.

SESSION 5: Paediatric clinical studies

Reported by Carolyn Hynes, Director, Global Regulatory Affairs Strategic Policy & Support, Johnson & Johnson Pharmaceuticals Group

Paediatric clinical trials, including study feasibility and long-term safety monitoring, was the focus of Session 5 chaired by **Agnès Saint Raymond, EMA** and **Angelika Joos, Merck**. The opening presentation by **Richard Veselý** and **Emma Sala Soriano** from the **EMA Paediatric Team** provided an overview of paediatric investigation plans (PIPs) in paediatric rheumatology, a complex area where there are many different types of disease. Juvenile idiopathic arthritis (JIA), the most common form of persistent arthritis in children, has had the greatest number of PIP applications to date. A comparison was presented of the age ranges for plans and waivers in the three main types of JIA, comparing what was initially proposed versus what was finally approved. In most cases there was agreement, although for a couple of PIPs the age groups covered by a waiver were reduced following assessment.

The feasibility of paediatric clinical trials was addressed by presentations from **Philippa Smith-Marshall, PharmaNet**, and **Chantal Belorgey, Afssaps**. The numerous resources available to sponsor companies to undertake a feasibility assessment was reviewed, and the important role that paediatric networks can play in this process was highlighted. When conducting feasibility studies, the considerations for sponsors include the resources, facilities and experience of the site as well as availability of the required patient population.

NCAs have the challenge of coordinating paediatric activities where the PIP is agreed by a central group (PDCO) but where clinical trials are authorised at the national level. In terms of the clinical trial authorisation (CTA) assessment, it was noted that, where available, a PIP summary report is very useful. However, these reports can be complex and CTA assessment could be facilitated if a final summary with the last version of clinical trial synopses as agreed by the PDCO could be provided. Greater collaboration between the PDCO and NCAs (via the Heads of Medicines Agencies Clinical Trials Facilitation Group (CTFG)) would be of benefit in assessing paediatric trials.

Long term drug safety, ie, the effects of chronic drug use or the delayed effects of drugs in children, was discussed by **Miriam Sturkenboom, Erasmus University Medical Center**. This is an important

area to consider, especially since many paediatric clinical trials are not suitable to address long-term safety issues since they are often small (<100 subjects) or too short (< 1 year) to detect ADRs. Data mining of EU medical databases is one way to specifically target children and investigate long-term effects. Methods in drug safety evaluation have evolved greatly in recent years, and there is a big movement to connect different European population-based healthcare databases in order to generate large-scale paediatric information.

SESSION 6: Clinical trials

Reported by Carolyn Hynes, Director, Global Regulatory Affairs Strategic Policy & Support, Johnson & Johnson Pharmaceuticals Group

Chaired by **Beatrice Oberle-Rolle**, Nobel Biocare, and **Fergus Sweeney**, EMA, this session provided an update on recent developments in relation to the conduct of clinical trials in Europe.

The voluntary harmonisation procedure (VHP) was the subject of the first presentation by **Hartmut Krafft**, Paul-Ehrlich Institute. The VHP, a pilot procedure initiated in January 2009 by the CTFG, offers a coordinated assessment of CTA applications for multinational trials. This in turn provides applicants with more harmonised and timely CTA approvals. Experience to date with the VHP has been fairly limited. Twenty applications went through VHP between April and August 2009, of which 11 were accelerated applications (at the proposal of the EMA) for pandemic influenza vaccines. The CTFG has recently made modifications to the VHP in order to further improve the process, and the guideline on the Heads of Medicines Agencies website is expected to be updated shortly to reflect these changes.

The experiences of one of the first companies to try out the VHP were shared in a presentation by **Elmar Schmitt**, Merck Serono. Overall it was a positive experience, with good collaboration with the CTFG resulting in timely health authority approvals. Internal resources and workloads were reduced compared with using the standard national submission process. In the Q&A session it was confirmed that Poland and the Netherlands are not taking part in the VHP, however it was noted that for all other member states, it would be an exception not to participate in a VHP.

The progress the CTFG has made with the safety monitoring of clinical trials was covered in a presentation by **Chantal Belorgey**, Afssaps. One of the outstanding issues with the implementation of the clinical trials Directive is that reporting of suspected unexpected serious adverse reactions (SUSARs) and the content of the annual safety report (ASR) are not harmonised across EU member states. Two CTFG working groups are addressing this issue. The subgroup on clinical trial safety and the clinical trials subgroup of the EudraVigilance working group have both provided input and recommendations for changes to the EC guidance which are planned for later this year.

Fergus Sweeney provided an update on transparency of clinical trial information in the context of the EudraCT database which is currently at version 7. By mid-2010, EudraCT version 8 will be rolled out, which will start to make protocol-related information public at the time of CTA approval. One of the key issues for the future will be that when data are placed into the public domain, it is essential that members of the public are able to find the relevant information. Consequently, the EMA has started discussions with patients and healthcare professionals about what the public part of EudraCT will look like and how information should be presented.

SESSION 7:

Revision of the variation regulation – key new principles

Reported by Claire Pomeroy, Senior Regulatory Affairs Executive, TRAC Services Ltd, UK

This session was co-chaired by three presenters. **Dr Peter Bachmann**, European and International Regulatory Affairs, BfArM, Germany and **CMD(h) member** introduced the topic of key provisions relating to the new Variation Regulation (EC) No 1234/2008. The objectives of the regulation are to be simple, clear, flexible, reduce administrative burden and adapt to ICH concepts without compromising human and animal health. Delegates were reminded that knowledge of the current system should not be forgotten as it will form the backbone of the future regulation.

Dr Hilde Boon, Scientific Administrator, EMA, began with the status of the variations legislation. The final 'draft' guideline was published on the EC website on 30 November 2009 and signalled the countdown to implementation of the new Regulation on 1 January 2010 for products authorised via MRP, DCP and CP. Dr Boon advised that this draft is suitable for stakeholders to use to start preparing for the implementation. She clarified that current regulations would continue to apply to any variations submitted before 1 January 2010. The panel appreciated that the timelines were tight and would be a challenge for the industry. Dr Boon then discussed the classification rules and how 'unforeseen' variations will be reclassified as default Type IB rather than Type II. Using the 'classification guideline' she provided an example using a decision-tree approach.

Dr Bachmann explained how variation grouping will be possible to combine different variations relating to one marketing authorisation (MA) owned by the same holder, if notified at the same time, to the same relevant authority in one application. These groups will be handled according to the highest variation classification. Type IA or IA_N variations may, however, be grouped across MAs. The introduction of Type IA Periodic Reporting ('Annual Report') will only apply to one MA. It was stressed that grouped variations must be meaningful to be reviewed simultaneously (ie, the changes must be consequential or related).

Dr Boon continued the presentation with worksharing practices, ie, the possibility to combine the same variation(s) relating to more than one MA of the same marketing authorisation holder (MAH) in one application leading to one assessment and outcome. There will be no pre-condition that product dossiers are harmonised, only that the same final outcome of the variation is expected. It was highlighted that line extensions are excluded from worksharing.

Ms Fiona Reekie, Director, Global Regulatory Affairs, Johnson & Johnson Pharmaceuticals, UK and EFPIA provided the industry perspective and welcomed the changes. Fewer burdens are expected on both company and authority resources and more consistent outcomes are expected. Changes will be implemented more quickly as a result of introducing Type IB default variations. She anticipates there will be few requests for amendments to Type II but there are concerns that requests for upgrades would delay the start of MRP procedures, etc. Regarding grouping, Ms Reekie welcomed the fact that negative assessment of single changes will not mean that the whole group is rejected, and RMSs can decide on potential implementation of agreed individual changes. Concerns are that authorities may not agree with decisions for groupings, as there may be different opinions on what is considered a 'meaningful' grouping for assessment. Likewise, there is worry regarding

the acceptance of worksharing request justifications and implementation of reference authority opinion by CMSs. Ms Reekie concluded that the new regulation will provide more opportunity for strategic thinking and planning for companies. She emphasised that harmonised and rapid implementation for national systems is required to ensure the industry and agencies can benefit from the new regulations.

SESSION 8:

CHMP achievements and challenges

Reported by Carol Walker, TOPRA Member (Industry)

The final session was chaired by Liz Gifford, Director, Global Regulatory Affairs, GlaxoSmithKline, UK and Eric Abadie, Chair of CHMP, Afssaps, France. Presenters reviewed the CHMP's operations, achievements and successes as well as the challenges faced by the CHMP and its working parties and other groups.

Alan Morrison, Vice President of International Regulatory Affairs and Safety, Amgen, feels that the CHMP has been successful, with timely approvals of approximately 12.5 months and robust scientific assessment. Specifically, Mr Morrison feels that certain aspects of the scientific advice (SA) procedure work well in terms of content and scientific delivery, and advice is generally predictive of CHMP questions. He said the lack of choice of Rapporteur does not reduce the review quality and that scientific advisory groups (SAGs) dealt with issues and CHMP questions very well. Mr Morrison suggested areas for improvement: efficiency, SA cost and timelines, finalisation of product information, optimisation of the risk management system and refinement of the PIP procedure and increased use of parallel SA. He called for even greater Agency transparency and would welcome convergence between the US and EU regulators.

Anthony Humphries, Head of Sector, Regulatory Affairs and Organisational Support, Post-Authorisation Evaluation of Medicines for Human Use, EMA, provided information on the heavy CHMP workload – the committee often works until 8.00pm or later during the CHMP week. The increasing number of generics applications is, he says, unsurprising but it has raised workloads significantly. Mr Humphries hailed SA as a success, adding that it does not guarantee approval but is beneficial when companies follow the advice.

Xavier Luria, Head of Safety and Efficacy of Medicines, EMA, gave an update on the CHMP working parties and SAGs. He particularly focused on proposed future SAG activities; for example, inviting additional external experts and patient representatives and improving planning and communications.

Session Chair Eric Abadie discussed ongoing projects from the CHMP Work Plan. The Work Plan includes several current priorities: benefit-risk assessment methodology, CHMP/PDCO interaction, relations with health technology assessment (HTA) bodies and European public assessment report (EPAR) improvement.

Ian Hudson, Director of Licensing, MHRA, UK, was disappointed that parallel SA and accelerated review seemed underutilised. He said that delays in the second half of the CP are less common now and timings are generally consistent, although there are occasional GCP issues or late safety issues. Dr Hudson acknowledged that the Agency could improve its communication with companies, but he noted that it already meets with companies regularly.

In conclusion, although some areas for improvement exist, the CHMP is doing well despite very high workload.



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