



Making Medicines Affordable

EGA Conference

highlights

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REGULATORY & SCIENTIFIC AFFAIRS

EGA and Medicines Authorities Vow Joint Effort to Develop Greater Regulatory Efficiency for Generic Medicines

In her opening remarks to the 7th EGA Regulatory & Scientific Affairs Conference, **JYTTE LYNGVIG**, Head of the Danish Medicines Agency and Chair of the Heads of Agencies Management Board, told delegates



JYTTE LYNGVIG
Danish Medicines Agency

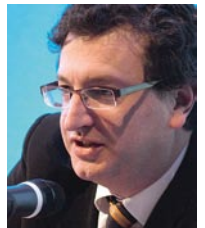
that for the medicines authorities, the participants at the EGA Conference are an important audience. Ms Lyngvig recognised the serious problem of resources in running the medicines approvals procedures, and said it was important for industry and the authorities to work together on improving the pharmaceutical regulatory system with the means at hand.

Lyngvig reported that a letter from the EGA recommending specific actions to remedy the current situation of resources at the agencies had formed the basis of discussions at the Heads of Agencies meeting in January. At the meeting a special *ad-hoc* HMA-CMD taskforce was created to look into details of the EGA's recommendations and to begin discussions with all industry partners. Initial thoughts will be presented in April, with a more detailed report to follow in July.

THE PANELLISTS of the opening session, including leading representatives from the National Medicines Agencies, the EMEA, the European Commission and the generic medicines industry, in turn presented their

vision and ideas on developing a more efficient European regulatory system for pharmaceuticals. All acknowledged that a more efficient use of available resources has become critical.

GREG PERRY, Director General, European Generic medicines Association, said the EGA has identified the lack of resources available to the Competent Authorities as a significant obstacle to the introduction of new generic medicines onto EU markets. He highlighted the long delays in obtaining a date for submitting an application and the limited availability of the National Medicines Agencies to serve as the Reference Member State. The EGA recognises that new countries have started to act in this capacity in 2007, but notes that the main workload is still covered by only four agencies.



GREG PERRY
EGA

JEAN MARIMBERT, Director General, Afssaps, agreed that operating the regulatory process efficiently is one of the biggest challenges facing national authorities. Deciding how best to use resources always creates a dilemma.

Purely national applications form the largest volume of agency work. In addition, agencies contribute to the Centralised Procedure, operate and coordinate the Decentralised and Mutual Recognition Procedures, and support multilateral activities, like the WHO. They are also having to cope with expanded workloads resulting from new legislation. In countries like

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"The lack of resources available to the competent authorities is a significant obstacle to the introduction of new generic medicines onto EU markets. We must work together to find a solution."

Greg Perry, Director General, EGA

INSIDE: Upcoming Legislation

- ★ Pharmacovigilance Framework
- ★ Bioequivalence Guideline
- ★ Variations Regulations



Heads of EU Medicines Agencies Speak Out at EGA Conference

Heads of European National Medicines Agencies in a lively exchange with other panelists during the opening session of the 7th EGA Regulatory & Scientific Affairs Conference. Pictured (left to right): Susan De Stasio, EGA, Aginus Kalis, Dutch MEB, Martin Terberger, European Commission, Thomas Lönngrén, EMEA, Jean Marimbert, Afssaps France, Jytte Lyngvig, Danish Medicines Agency, and Greg Perry, EGA.

Medicines Authorities & Industry Reorganise in Face of Expanding Workloads and Limited Resources

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France, with restrictions on hiring, agencies are working to re-engineer their organisations and to rethink operations to prioritise activities in terms of risk/benefit and added value to public health.

THOMAS LÖNNGREN, Executive Director, European Medicines Agency, noted that the way the network of the 27 EU Member States is working lends credit to the system and shows what can be achieved through European cooperation. The EMEA's success of the past 15 years has only been possible through the collaboration between the national agencies, the EMEA, and the European Commission with the support of the European Parliament.

Lönngren reported that the EMEA has had very positive early experience with the centralised procedure for generic medicines. He also pointed out that the EU has become the world's leader in biosimilar medicines, and that the EMEA has maintained a very constructive dialogue with the EGA both on biosimilar and generic medicines, sharing knowledge and experience on how best to handle applications.

AGINUS KALIS, Head, Dutch Medicines Evaluation Board, said the large number of European applications had not been foreseen. New telematics tools are being introduced to better manage the authorisation process, but this will demand greater discipline both from the authorities and from industry.

SUSAN DE STASIO, Director of Regulatory Affairs, Arrow Generics, and Chair, EGA Scientific & Regulatory Affairs Committee, observed that industry is caught in a vicious circle regarding booking submission slots, as very few are available for 2009. The industry needs to be confident it can launch its products on time and is pleased to hear the commitment from the authorities to address this issue. The creation of a task force is seen as a constructive approach and is reassuring. We need to understand the constraints on both sides and work together toward a solution, she concluded.

MARTIN TERBERGER, Head of Pharmaceuticals Unit, DG Enterprise, European Commission, reported that the European Commission has also noticed that the number of Centralised Procedure applications increased last year by 30%. The issue of resources applies to the EC, too, he said. The Commission has proposed several important projects within the framework of better regulation, including: simplifying the variations regulations, rationalising the pharmacovigilance system, and harmonising certain requirements under transatlantic cooperation. A major objective of these initiatives should be to focus not only on the efficiency of the system, but also on their effectiveness for protecting public health. ■

New Decentralised Procedure a Success, Industry Advised on Speeding Up Procedures

Christa Wirthumer-Hoche, Deputy Head, AGES PharmMed, Austria, announced the success of the new Decentralised Procedure. The number of procedures finalised in 2007 under the DCP rose significantly over 2006 and 80% of applications under the DCP were for generic medicines. Importantly, the number of referrals and withdrawals have decreased considerably despite the larger numbers.

The majority of procedures are run by only four agencies, but most agencies have expressed a willingness to serve as the Reference Member State in the future. And while all are committed to improving the system, companies can also do their part by planning submissions more thoroughly. From an industry perspective, booking slots too far in advance does not reflect the actual status of product development and companies can run the risk of submitting premature dossiers.

Careful preparation of dossiers also helps to ensure a smooth and rapid procedure, as does submitting translations of the SmPC and the patient leaflet (PIL) on time. Requesting a duplicate application during the procedure or a repeat use immediately after the first round of the DCP must be avoided. ■

Centralised Procedure for Generic Medicines Stumbles Over Use Patents & Multiple Fees

Zaide Frias and **Tony Humphreys** of the EMEA's Regulatory Affairs and Organisational Support Department discussed the centralised procedure (CP) for generic and hybrid applications to complement the mutual recognition and decentralised procedures (MRP/DCP).

The regulatory framework is now almost complete, but use patents on originator reference products remain a serious stumbling block for generic medicines. This patented information can be 'carved out' of applications at national level under the MRP/DCP. Under the CP, however, a generics applicant must take either the 'lowest common denominator' approach, including only indications or dosage forms in the summary of product characteristics (SmPC) that are not under patent in any Member State, or the 'multiple applications' approach, filing a different SmPC for each application.

Fees for multiple applications, crucial to deciding a registration strategy, have not yet been decided. The EGA feels they should not exceed the fee charged for a Type II Variation. ■



Jean Marimbert
Afsapps - France



Thomas Lönngren
EMEA

“For the medicines authorities, the participants at the EGA Conference are an important audience.”
Jytte Lyngvig



Martin Terberger
European Commission



Aginus Kalis
MEB - Netherlands

Key Recommendations for Regulatory Efficiency

Generic Medicines Industry to the Authorities

- **ELIMINATE** parallel full assessments carried out by some Concerned Member States.
- **INTENSIFY** worksharing between national competent authorities
- **INCREASE** the contribution of Member States to the system as Reference Member States.
- **ESTABLISH** closer cooperation between new assessors and more experienced experts through twinning projects or peer review.
- **PROVIDE** more training opportunities for newer less experienced experts to help harmonise assessments.

Medicines Authorities to the Industry

- **PLAN** commercial strategies clearly at the beginning. Decide early about duplicate applications and in which Member States you want to file.
- **BOOK** only one slot per product and avoid booking too far in advance.
- **INFORM** agencies when development plans change and a booking slot will not be used.
- **COMPLY** carefully with all terms and requirements when preparing dossiers.
- **SUBMIT** a full dossier from the start, rather than expecting to add supplementary information later on.



European Commission's Two-Point "Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance"

The 1st EGA Pharmacovigilance Discussion Forum focused on the European Commission's two-pronged strategy on Europe's pharmacovigilance system, with proposals to adapt the legal framework for the future while striving to meet current challenges by improving how the present system is implemented by the authorities and industry today.

Peter Arlett, Principal Administrator at the Pharmaceutical Unit, DG Enterprise and Industry of the European Commission, emphasised that the Commission, regulators and industry all share joint responsibility in ensuring that the EU pharmacovigilance system remains fit for the future. The legal framework should reflect the advances of science, information technology and the new challenges linked to EU enlargement.

Quoting from the consultation paper, Mr Arlett said that the lack of harmonisation in pharmacovigilance requirements amongst Member States has led to today's complex reporting requirements for industry and clearly interferes with the functioning of the single market for medicinal products. All stakeholders have called for a stronger, more rationalised system.

THE COMMISSION'S KEY PROPOSALS touch on:

- EU decision making on safety issues,
- The roles and responsibilities of industry and regulators,
- Company pharmacovigilance systems,
- Risk management planning,
- Non-interventional safety studies,
- The reporting of adverse drug reaction (ADR) case reports,
- Periodic safety update reports (PSUR), and
- Transparency and communication.

Harmonised Birthdates (HBD) and Public Safety Update Reports (PSUR)

Pim van der Giesen, of the Dutch Medicines Evaluation Board and initiator of the EU Harmonised Birthdates Initiative, highlighted that HBDs and related Data Lock Points (DLPs) have been published for some 650 substances authorised since 1976, and that the target for publishing the dates for older substances remains June 2008. The project aims to harmonise safety information.

He observed that PSUR synchronisation and worksharing between national agencies is a complex exercise, and therefore the guidance documents will be further updated as practical experience accrues. He also touched on the guidance for Marketing Authorisation Holders, that clarifies the issue of Core Safety Profiles (CSP), which can be implemented across the EU.

Marina Belle, PSUR Manager Sandoz, presented the EGA perspective on the experience, concluding that EGA member companies are satisfied with the clear progress made last year, and that they look forward to an improved process for renewal harmonisation, acceptance of HBDs in non-EU countries, further nominations of PSUR Reference Member States, and to a clear process for amending the published lists. ■

EGA RESPONSE

Wendy Huisman, Teva Pharmaceuticals/EGA, acknowledged these proposals have been well received. The EGA supports strengthening and rationalising pharmacovigilance, although certain specific issues need further discussion, such as:

- Periodic Safety Update Reports (PSURs) for older substances, which are still considered useful, but should be risk-based.
- Pharmacovigilance System Master File (PSMF), which should be stored centrally, while remaining accessible to the agencies.
- Worldwide literature search, which should be performed centrally and be downloadable by industry in ICH format.
- New section on key safety messages in Patient Information Leaflets (PILs), which may lead to non-compliance with treatments and to issues of liability.
- Risk management plans, which need further clarification.
- Identification of biological products, which should not be subject to national requirements to avoid new disharmonies.

Huisman concluded with praise for the Commission's proposals, saying that in general they maintain today's high level of pharmacovigilance, while moving it a step forward in efficiency. ■

EU LEGISLATIVE PIPELINE

Variations Regulations

Maintaining a marketing authorisation (MA) consumes significant resources of the medicines authorities and industry. A medium-sized company submitted some 4000 variations in 2006, and a large company up to 19,000. Many are purely administrative, not affecting public health. News of this revision is welcomed by all stakeholders.

Nicolas Rossignol, European Commission, DG Enterprise, Pharmaceuticals Unit, explained that the legislation will be adopted in three parts:

- Directive 2001/83/EC will be modified to include purely national MAs in the Variations Regulation. The proposal will be published in April 2008 and is expected to be adopted smoothly under co-decision before the European elections in 2009.
- The technical details of the variations procedure will be agreed through comotology in 2008 for implementation after a 12-18 month transition. These rules will extend to purely national authorisations in 2010/11.
- The legally binding guideline describing the classification of variations and conditions for applicants will be modified by technical committee and published with the Regulation. ■

Bioequivalence Guideline

Generic medicines must undergo bioequivalence studies to demonstrate their therapeutic equivalence to the originator reference product in terms of rate and extent of absorption in the body. The existing EU guideline governing bioequivalence is often subject to differing interpretation between Member States due to a lack of consensus on critical parts of the document. This leads to disagreement amongst the authorities during registration procedures and to referrals which delay approval.

A new guideline is currently being prepared to clarify and simplify these procedures. Jan Welink, of the Dutch MEB, said a first draft is now under discussion in the pharmacokinetics subgroup of the EMEA's Efficiency Working Party.

Truus Janse-de Hoog, Chair of the CMD(h), announced that the 2nd Joint EGA/CMD Bioequivalence Workshop will be organised in Paris on 8 October. Mr Welink, confirmed that the EWP is working on a final draft in time for this exchange of expertise with EGA members. "We hope to reach a consensus, with a new guideline understandable for applicants and for the Member States, and that we can reduce the number of referrals..." he said. ■

Pharmacovigilance Framework

Revising the EU Pharmacovigilance Framework has been set as a priority for the European Commission as no systematic review of these provisions took place during the 2001 Review of EU pharmaceutical legislation.

Since then, twelve new countries have joined the EU, technology has advanced, and European society has not ceased to evolve. It is important that pharmacovigilance legislation continues to meet today's realities and to ensure that the system remains fit for the future.

The European Commission launched a consultation in December 2007 on draft proposals to modify Directive 2001/83/EC and Regulation 726/2004 which make up the Framework. The Commission plans to approve the proposals during the 4th quarter 2008, sending them to the European Council and Parliament under co-decision. The new framework could be implemented as early as 2011 (see the article above for more details). ■

Weak Patents with No Inventive Step Undermine Innovation & Competition

The EGA is calling for greater patent quality through more rigorous assessment of the inventive step. In his opening address to the 4th EGA Legal Affairs Forum, **Greg Perry**, EGA Director General, reiterated the association's call to ensure that patents are only granted when supported by sound evidence.

"Weak patents, based on inadequate examination and inconsistent criteria, must be eliminated for the public good", Mr Perry said. He added that failures to enforce solid patent criteria damages competition and lead to less innovation and a loss of savings for healthcare systems.

The 'inventive step' requirement currently represents the most problematic area of patentability. Only by changing the awareness of patent examiners and strengthening the quality assurance mechanisms at the European Patent Office can the

assessment of the inventive step be reinforced and made more reliable.

Mr Reto Hilty, Director of the Max-Planck Institute in Munich, insisted in his presentation that the patent system must not be used to restrict competition from generic medicines by approving weak patent applications.

Whilst patents are clearly important for encouraging innovation, an EU patent system that is too permissive in granting patent rights will prevent generic competition, restrict access to medicines through decreased affordability, and will ultimately discourage real innovation in the pharmaceutical sector.

When patents are aimed solely at excluding competitors from the markets, patent quality becomes crucial to ensuring the rights of consumers and patients. ■

Safeguard Measures Needed Against Potential Abuse of Interim Injunctions

Injunctions are a strong weapon in the armoury of the patentee, according to **David Bloom**, senior associate of the Life Sciences Team, Roiter Zucker. As long as the courts act fairly and efficiently, he said, interim injunctions provide a sensible way of dealing with the difficult issue of potential infringement of IP rights.

But **Greg Perry** warned generic medicines producers to beware of EC Directive 2004/48/EC. This legislation, he pointed out, lays down harsh measures to enforce IP rights and could have a huge impact on competition if abused and if the safeguards provided are not applied.

If article 3.2 of the Directive—which says: "Those measures shall be applied in such a manner as to avoid the creation of barriers to legitimate trade and to provide for safeguards against their

abuse"—is not applied, injunctions will be easier to obtain on lower levels of proof. Whilst the risks are expected to remain low in well-established courts in the United Kingdom, the Netherlands, and Germany, the near future could see increasing abuse of the Directive in others.

Yehudah Livneh, general patent counsel for Teva Pharmaceuticals, maintained that protection against abusive litigation is needed as a safeguard at the EU level.

Protective letters represent only a partial solution, he said, as they are time consuming and expensive, and are potentially required for every marketing authorisation in every country for every product. More efficient solutions should be developed and implemented as quickly as possible, he concluded. ■

European Commission Opposes IP Abuse, Announces New European Patent Court

Dr Jens Gaster, DG Internal Market, European Commission, told the Forum that the Commission is actively involved in patent issues and enjoys special observer status at the Administrative Council of the European Patent Office. He emphasised that the Commission opposes patent trolls and patent thickets, and that Art. 82 of the Treaty is a sharp and effective weapon in fighting unlawful monopolies, although it can take time to yield results.

Mr Gaster also said he believes in providing incentives to EPO examiners to refuse patents based on

weak or deficient applications, and can already see some signs of positive change in that direction.

The EPO Council, for example, has recently introduced a new higher fees scale aimed at curtailing abusive applications.

He announced there will now be no European Patent Litigation Agreement (EPLA). Instead, the European Council has approved plans to create a European Patent Court as a specialised body linked to the European Court of Justice in Luxembourg.

This new body will only be responsible for hearing cases on the validity of patents. ■

Patent Linkage Remains a Major Threat in Europe

The EGA reminded the Forum that patent linkage has no basis in European law and is not part of the *aquis communautaire*. In addition, it creates an impossible situation for regulatory authorities who lack the mission, resources and legal expertise to assess the validity of patents.

The EGA has helped to halt patent linkage in Belgium, Bulgaria, Rumania, France, and Hungary. But the Slovak Republic maintains its provision entitling the State Institute to reject the marketing application of a generic medicine if the reference product is protected by patent or SPC. The EGA's appeal to the European Commission on this issue is pending.

In the meantime, patent linkage continues to threaten in Portugal, Sweden and Italy. All attempts to introduce such legislation in the EU must be closely monitored. ■

Complicated SPCs for Paediatric Indications

European Patent Attorney, **Robert Stephen**, recommended greater transparency with regard to the complicated situation of SPC extensions for paediatric products, which only require a six-month notification period. Mr Stephen also noted that no SPCs will be granted for second medical use claims where the product has received prior authorisation as a medicinal product. ■

No Room for Patents in EU IP 'Criminal' Enforcement

The draft 'IP Enforcement' Directive establishes criminal penalties to enforce all IP rights, including patents. The measure raises fears that uncertainty over the validity of patents and the risk of prosecution will inhibit innovation and competition from generic medicines. **Greg Perry**, quoted NOKIA's IP Director, who said: "With this law, even if I'm certain the existing patent is no good, the manager would be criminally liable."

Patents were excluded by the European Parliament in first reading, but to ward off this threat, industry must monitor the Directive closely in the EU institutions to keep patents out of its scope. ■

Counterfeiting Medicines Not a Patents Issue

Greg Perry stressed the EGA's conviction that the counterfeiting of medicines is not an issue of patents, but rather of trademarks. Counterfeiting must not become an excuse to increase patent protection on pharmaceuticals in Europe.

Treating generic medicines on a par with potentially dangerous counterfeits in cases of alleged patent infringement will only hinder patient access to affordable medicines and will not increase public safety. ■

Making Medicines Affordable



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The EGA is the official representative body of the European generic medicines industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.