



Making Medicines Affordable

EGA Conference highlights

EGA REGULATORY DIALOGUE

2nd EMEA-EGA INFORMATION DAY

European Generic Medicines Industry and Regulators Build Dialogue for Increased Understanding & Cooperation

CENTRALISED PROCEDURE: A CONFIRMED SUCCESS FOR GENERIC & BIOSIMILAR MEDICINES

THOMAS LÖNNGREN, executive director, EMEA, announced in his introduction that the number of generic applications to the EMEA has doubled every year since 2006 when they were first accepted. He indicated that 2008-2009 would see further significant increases in the number of generic and biosimilar applications.

"Twenty per cent of all EMEA applications will be from the generics industry in the years to come", he said. He also praised the EU approach to biosimilar products, which are successors to originator biopharmaceuticals. **"Biosimilars is a success story and Europe will continue to lead in the development of guidelines in this area,"** Lönngren said.

GREG PERRY, director general, EGA, took advantage of the Info Day to lay out the EGA's long term vision for the industry, listing the main challenges for the next round of legislation (see box). Perry also requested the EMEA's support for the 'EU Biosimilar philosophy' at international level and in discussions with the WHO. He emphasised the need for open discussion on global development for biosimilar medicines. "Cutting development costs for

biosimilar medicines will increase affordability and improve access to high quality medicines for more patients worldwide", he said.

Perry further commented that, "the Centralised Procedure is working well both for generic and biosimilar medicines, although some future fine-tuning to it is still necessary."



THOMAS LÖNNGREN
Executive Director EMEA

JOSE RAMON COZAR RUIZ and **EVANGELOS KOTZAGIORGIS**, EMEA, covered the past two years of positive experience in handling generic products of centrally authorised reference products. "Both the EMEA and applicants are on a steep learning curve", they said, commenting later that "Pre-Submission Meetings with applicants are a vital opportunity for applicants to obtain procedural, regulatory and legal advice from the EMEA."

A major challenge in the future will be to improve collaboration between the national Competent Authorities and the EMEA to ensure consistency of assessment, to remove the risk of divergence between national & centralised evaluations of the same dossier, and thereby to increase the efficiency of the regulatory network.

UPCOMING LEGISLATIVE CHALLENGES

- a) Accepting a different Summary of Product Characteristics (SmPC) in a single procedure in the case of usage patents
- b) Allowing flexibility in naming
- c) Revising the restrictions for using the Centralised Procedure in order to increase access to the EEA market
- d) Reducing fees for normal duplicate applications

ARIELLE NORTH, EMEA, presented the new fees schedule for initial applications, post-authorisation activities (extensions, variations, renewals), and the annual fees for multiple applications of generic, hybrid and biosimilar products on usage patents grounds. The full or partial exemption of fees, published in Annex VII of the latest rules on fees payable to the EMEA, are applicable for as long as the concerned marketing authorisation is affected by usage patent(s) pertaining to indication(s) and/or dosage forms. **The fee reduction for second and subsequent applications is about 80% of the total fee. Additional strengths, pharmaceutical forms, and presentations are totally exempt of fees.** ■

EGA REGULATORY DIALOGUE

The EGA has engaged in a series of meetings with European National Medicines Agencies to maintain an on-going dialogue between industry and regulators. The initiative is designed to provide opportunities to assess legal and regulatory measures and to increase cooperation and mutual understanding of each other's concerns, needs, and priorities. Highlights from four such encounters are presented here.



CANARY WHARF, London | Home of EMEA Headquarters.

The Role of AFSSAPS in Generic Medicines Evaluations, in European Procedures and in Supervising Quality, Safety & Efficacy

COOPERATION AND INTERDEPENDENCE

Greg Perry, director general, EGA, opened the AFSSAPS-EGA Info Day, the first in a series of meetings with National Medicines Agencies designed to increase cooperation and mutual understanding of each other's needs, requirements and priorities. Perry pointed out that generic medicines constitute 80% of applications in the Mutual Recognition/Decentralised Procedures (MR/DCP), a fact that creates close interdependence between the agencies and the generic medicines industry.

Ensuring adequate resources to the agencies and efficient 'slot' allocation was noted as the single biggest concern for the generic medicines industry. "On the one hand", Perry said, "we need flexibility from the agencies on the timing of slots. On the other hand, the industry needs to end its current practice of double booking of slots. These two issues are completely related. Working together to resolve them in the short term will help open up a number of slots quickly."

Jean Marimbert, director general, Afssaps, welcomed the Info Day as a means to increase mutual confidence and understanding. He noted that his agency takes some 80,000 decisions each year, covering a range of activities related to evaluations and inspections, but also to laboratory and control activities, and to a number of products, including pharmaceuticals and medical devices, as well as less classical items such as cosmetics and tattooing products. France currently plays a leading role at EU level and, Marimbert said, "We intend to keep investing in European procedures and work." Although he expects administrative burdens to decrease under the new variations regulation, his main challenge is to reconcile available resources with the demands of national and European activities (MR/DCP, CP). "We have embarked on an ambitious process." Marimbert explained, "We have to adapt. We have to solve the resources issues. We have to work at national level to become more efficient, more selective and more relevant in our interventions and actions. We have to work at the EU level with our colleagues to share some work to avoid overlapping."

GENERIC MEDICINES EVALUATION

Antoine Sawaya, Afssaps, addressing the regulatory and legal aspects of generics applications in France, clarified the situation for the applicability of the European reference product and the global marketing authorisation. In the case of use patents, he suggested the applicant should indicate to the Agency

procedures (MR/DCPs) in 2007 to 70 in 2008. To meet this objective Afssaps has recently undergone a thorough restructuring to achieve:

- better distribution of workloads,
- better resource allocation scheme, and
- better coordination between evaluation teams.

“ By combining more efficiency, more relevance at national level, and more common work at EU level, I am confident that we will find, at the end of the day, the solutions to solve the problems that preoccupy you and us. ”

Jean Marimbert, Afssaps



the sections of the SmPC still covered by patents. In a national procedure, the SmPC will be identical for the reference products and the generic medicine.

Héloïse Pham, Afssaps, compared the registration systems for new chemical entities and for generic medicines. She then presented the structure, composition, and operating mode of the Afssaps generic medicines unit, saying it had high levels of expertise, short assessment delays, consistent evaluation, and solid opinions based on pharmaceutical and biopharmaceutical evaluations.

Anne Gayot, Afssaps, in addressing the most frequently asked questions in deficiency letters related to generics applications, looked at each CTD section of the quality modules and emphasised on particular aspects related to active substances (ie, sterilisation process, validation data, stability data, polymorphism and granulometry).

To increase the chances of passing the regulatory assessment of bioequivalence, **Patrick Nicolas**, Afssaps, pointed out the need for industry to prepare high quality projects and to include even more careful and critical assessment of CROs and study data.

AFSSAPS IN EUROPEAN PROCEDURES

Alban Dhanani, Afssaps, explained that France has worked to increase its role as Reference Member State (RMS) for generic medicines applications from 32

SUPERVISING QUALITY, SAFETY AND EFFICACY

Pierre-Antoine Bonnet, Afssaps, described Afssaps' constant monitoring of the quality of medicines through ongoing laboratory control surveys. Comparative evaluations of the quality of the medicinal products and APIs within a Product Group are regularly performed. No significant differences have been identified between reference products and generic medicines. The quality of generic medicines on the French market is globally satisfactory.

Pierre-Henri Bertoye, Afssaps, reported that Afssaps evaluations and inspectorates have been reorganised to improve the overall coordination of the surveillance strategy. The control programme is based on risk-oriented prioritisation. No differences between generic and originator pharmaceutical companies have been reported. Inspections also contribute to quality improvements in the pharmacovigilance systems of individual companies. Bertoye advised the generic medicines industry to pay particular attention to pharmacovigilance reporting. Bertoye also said that the specific bioequivalence trials inspection programme for Good Clinical Practice (GCP) was initiated in 1995 and its priorities are established on the basis of risk-assessment. France has built solid expertise in the field of bioequivalence trials inspections and represents the main contact point for most of the inspectors in Europe. ■

Recommendations to Solve the Problem of Agency Resources

For the authorities:

- Increase the number of assessors available to examine applications.
- Eliminate full parallel assessments.
- Improve cooperation and coordination between Medicines Agencies.
- Build confidence between Member States.
- Increase the Member State contribution to the system as Reference Member State.

For industry:

- Book only one slot at a time per product and avoid booking too far in advance.
- Provide advance notice to agencies of commercial strategies, and warn the authorities when development plans change.
- Submit top-quality applications, with a complete dossier from the very beginning, complying fully with all terms and requirements.

“ We are here to cooperate with you and to work with you in anything we can do. ”

Greg Perry, EGA



Making Medicines Affordable

Meeting the European Challenge for the National Drug Regulatory Agencies and the Generic Medicines Industry

The EGA regularly brings regulators and industry representatives together to assess legal and regulatory measures in the EU and non-EU countries of South East Europe as part of its continuing dialogue between medicines authorities and industry from European countries who are not yet members of the EU.

The 4th EGA South East Europe Symposium was organised in Istanbul, Turkey in cooperation with the Pharmaceutical Manufacturers Association of Turkey (IEIS) and the Ministry of Health of Turkey. Previous events were held in Split, Bucharest and Sofia, all in conjunction with the host country's medicines authorities.

Participants included top-level representatives from the medicines and patent authorities from throughout the region, including Bulgaria, Croatia, Federation of Bosnia and Herzegovina, Hungary, Kosovo, Macedonia (FYROM), Montenegro, Republic of Srpska, Romania, Serbia, Slovenia, and Turkey. Some 40 representatives from governmental agencies took part in the event.

GREG PERRY, director general EGA, remarked that such an enthusiastic participation reflected the region's eagerness to work jointly on issues of common European interest and its commitment to sustainable, quality healthcare. Mr Perry emphasised the critical role of generic medicines in the region's ability to pro-

vide affordable healthcare to citizens. For this reason he advocated caution when considering the "extra-curricular" legal and regulatory provisions being promoted by some pharmaceutical sectors. He particularly warned against adopting new data exclusivity provisions which would negatively impact the rapid availability of generic medicines to patients. Similarly, Mr Perry reminded the delegates that supplementary protection certificates (SPCs) must only be introduced as part of an EU membership package, and he reiterated that any patent linkage provisions were totally contrary to EU regulatory procedures and would only deprive patients of the medicinal care they deserve.

MAHMUT TOKAC, director general, Turkish General Directorate of Pharmaceuticals, commented during the first part of the symposium on the impact of EU negotiations on the pharmaceutical sector in Turkey, followed by a presentation from **EDA CINDOGLU**, Turkish Ministry of Health, on planned changes to Turkish pharmaceutical law.

The representatives of national authorities from Croatia, Federation of Bosnia and Herzegovina, Kosovo, Macedonia (FYROM), Montenegro, Republic of Srpska and Serbia presented an overview of the regulatory environment for generic medicines in South East European countries and plans for legislative changes in view of harmonisation with EU law.



ROUND TABLE DISCUSSION

The authorities and selected industry representatives from the region continued the round table discussion in a closed session with the principle objective of encouraging cooperation and improving regulatory procedures in the region. Industry representatives identified potential areas for improvement related to the:

- Certificate for Pharmaceutical Products and Marketing Authorisation requirements from the "country of origin";
- Choice of the Reference Product for a generic medicine application;
- Practices related to the testing of samples as the part of MA process and post-authorisation control;
- Procedures for updating dossiers.

In view of future changes in the EU regulatory and legal environment related to the new variations system, revision of the pharmacovigilance system, introduction of new anti-counterfeit measures, and industry information to patients, industry expressed a desire to follow the current EU legislative processes in the non-EU countries and to adopt certain elements simultaneously in the SEE region. ■



◀ Just three of the many national medicines authorities participating in the 4th EGA South East Europe Symposium in Istanbul: Eda Cindoglu of Turkey, Tamás Paál of Hungary, and Vesna Koblar of Slovenia.

INDUSTRY RECOMMENDATIONS FOR NON-EU REGULATORS

Recommendations for Pharmacovigilance Reporting in non-EU Countries

- Harmonise PSUR cycles in line with the EU with the possibility of aligning with the harmonised birth date (HBD) in the EU.
- Introduce the provision for early renewal to bring the renewal application in line with the EU PSUR HBD.

For global companies with the same products registered in EU and non-EU countries this harmonised approach is the best way to deliver improved safety information to patients throughout Europe and will contribute to future harmonisation with the EU pharmacovigilance system.

Recommendations for Dossier Updates in non-EU Countries

- Manage the updating process to ensure an optimal and balanced use of the important resources it requires and to ensure other regulatory activities which foster rapid patient access to new generic medicines.
- Avoid unnecessary repetition of studies (accept earlier bioequivalence studies, justifications for biowaiver, etc).
- Focus on evaluating the risk/benefit ratio of medicines, not on dossier format (not compulsory in CTD).

Recommendations for Variations in non-EU Countries

- Harmonise the classification of variations and timelines in line with the new EU Variations Regulation.
- Introduce a "do and tell" variations scheme, with reporting within 12 months for type IA variations.

A harmonised system for implementing changes to the same products authorised in both EU and non-EU countries will greatly facilitate the logistics of manufacturing and supply for companies with global operations.

Recommendations for CPP and for the Requirements of the MA in the "Country of Origin"

- Accept equally the Certificate for Pharmaceutical Product (CPP) type A and CPP type B by regulatory authorities.
- Adapt national legislation in non-EU countries to the business model of companies operating on several markets (several production sites, dossier development for several MAHs, etc).
- Adopt a more flexible approach to the request for Marketing Authorisation (MA) in the "country of origin" in view of a company's regulatory and marketing strategies.

Guideline Revision, Regulatory Procedures and Good Practices: Paving the Way to an Even More Efficient Regulatory Framework



TRANSPARENCY & COORDINATION

Fabienne Bartoli, deputy director, Afssaps, and **Truus Janse-de-Hoog**, chair, CMD(h), welcomed the 2nd EGA-CMD(h) Symposium on Bioequivalence as an excellent means of promoting new guidelines through greater transparency for operators and more coordination between competent authorities. The CMD(h) is participating in this joint effort with the European generic medicines industry to develop and improve the interpretation of guidelines and standards within the bioequivalence arena.

DATA INTEGRITY, GCP & GLP INSPECTIONS

Louise Mawer, MHRA, and **Olivier Le Blaye**, Afssaps, reinforced the benefits of cooperation through greater transparency and joint review processes between assessors and inspectors, and through the harmonisation of procedures in the EU. Recent and future regulatory developments in the field of inspection are listed in the blue box below.

Janja Luksa, EGA, pointed to the need for a bio-analytical method validation guidance document.

EARLY & LATE DIALOGUE WITH AUTHORITIES: SCIENTIFIC ADVICE TO REFERRALS

Truus Janse-de-Hoog, chair, CMD(h), reported to industry that the authorities "... are open for early dialogue", and that the "RMS and CMSs could discuss potential referral issues" within the current framework.

Susan De Stasio, chair, EGA Regulatory & Scientific Affairs Committee, announced that industry

does not favour product specific guidance development, given the highly competitive nature of bioequivalence studies and designs.

John Warren, MHRA, reinforced the need for dialogue, saying "There are two rules for regulation: one is that we protect public health, the second rule is that we do not hinder industry."

Tania Meier and **Ulrike Poller**, BfARM, emphasised the increased need for developing products to treat conditions—such as chronic obstructive pulmonary disorders (COPD)—which are predicted to be the third cause of death by 2020. Their recommendations to applicants include the use of a step-wise decision-making process (revised guideline, see box) and the use of scientific advice.

Julie Maréchal, EGA, reported that EGA member companies are keen on more direct interaction with authorities. Earlier settlement could improve the predictability of the registration time frame and reduce the number of referrals.

THE BIOEQUIVALENCE GUIDELINE: OUTCOME OF THE REVISION

Tomas Salmonson, MPA, summarising the revision of the Bioequivalence Guideline, explained that "We moved into a [more] quality type guideline, away from [...] a scientific guideline." And insisted that it represents "a way of moving forward from disharmony." He clarified that until the revised guideline is finalised, "the old guideline applies."

Jan Welink, MEB, and **Jose Morais**, INFARMED, presented the fundamental changes introduced in

the revised guideline. Both referred to the intense debate required to reach a compromise and the necessary clarifications to limit interpretation. "We hope that this will lead to a consensus", Welink said. Both asked for timely feedback from industry.

Gerald Beuerle, EGA, particularly welcomed the clarifications made during the revision of the guideline and pointed out the newly introduced prescriptive approaches which might need reconsideration from the perspective of the generic medicines industry.

GUIDANCE FOR DEVELOPING LOCALLY ACTING PRODUCTS

Kevan Cassidy, co-chair, EGA Bioequivalence Working Group, said that "The generic companies [...] would like to counsel against guidelines that become so prescriptive that we are not allowed to make any scientific manoeuvres."

Andrea Laslop, AGES, commented that "Although this guideline is quite old, it still addresses in an appropriate way the major problems raised within the development of local treatment". Currently, the EWP has no current plan to revise the current Guideline on Locally Applied, Locally Acting Products (1995). However, other specific guidelines are revised on an ongoing basis. She advised applicants to seek scientific advice.

Vit Perlik, EGA, stressed the need to consider a revision of this guideline to accommodate recent technological developments and to address more specifically the many different pharmaceutical forms and medicinal products at stake. ■

Key Regulatory Guidance Document Information

RECENTLY ADOPTED

- Annex VII of the EMEA GCP Inspection Standard Operating Procedure | May 2008
- Draft Advice to Applicants, Sponsors, CROs adopted by the EMEA GCP IWG | Sept 2008
- Draft Q&A on IMP Packaging in BE Trials adopted by the EMEA GCP IWG | Sept 2008

UPCOMING DOCUMENTS

- Guideline on Orally Inhaled Products (Final) | January 2009
- Bioequivalence Guideline | Fall 2009
- Concept Paper on the Bioanalytical Method Validation Guideline | 2009

“ There are two rules for regulation: one is that we protect public health, the second rule is that we do not hinder industry. ”

John Warren, MHRA

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EUROPEAN GENERIC MEDICINES ASSOCIATION
Rue d'Arlon, 50 | B-1000 Brussels | Belgium
T: +32 (0)2 736 84 11 | F: +32 (0)2 736 74 38
www.egagenerics.com | info@egagenerics.com

The EGA is the official representative body of the European generic and biosimilar 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.

¹ BCS= Biopharmaceutical Classification System