Human & Veterinary Medicinal Products Regulation

Turkey's Road to EU Membership

22 - 23 October 2007

Barceló Eresin Topkapi, Istanbul, Turkey

Conference Committee

Project Leaders
Hans-Georg Wagner, European Medicines Agency, EMEA
Sylvie Bénéfice, European Medicines Agency, EMEA

Steering Committee Members
Mahmut Tokaç, Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*
Eda Cindoğlu, Ministry of Health, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*
Semra Yilmaz, Ministry of Agriculture and Rural Affairs, General Directorate of Protection and Control, *Turkey*
Olcay Türe Göksu, Ministry of Agriculture and Rural Affairs, General Directorate of Protection and Control, *Turkey*

EMEA representatives from:
- Pre-authorisation Evaluation of Medicines for Human Use
- Post-authorisation Evaluation of Medicines for Human Use
- Veterinary Medicines and Inspections
- Directorate
- Communications and Networking

Welcome to Istanbul!
İstanbul'a hoş geldiniz!

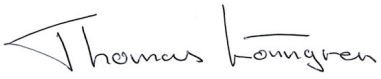
It is an honour to invite you, on behalf of the European Medicines Agency, to this major conference in Istanbul, Turkey.

In view of Turkey's potential accession to the European Union, this is a valuable opportunity for us to offer key information about legislative, procedural and scientific aspects of medicines regulation in the EU.

It is also a great opportunity for us to get to know our esteemed Turkish colleagues better, and to discuss with you in detail your views, expectations and reservations about the challenges and opportunities that lie ahead.

I am hopeful that this conference will help to pave the way for Turkey to become an equal partner in the European regulatory network in the future, and I look forward to welcoming you personally in Istanbul.

Best regards,



Thomas Lönngren
Conference Chairman
European Medicines Agency

The conference is funded by the multi-beneficiary programme for supporting the participation of Croatia and Turkey in EMEA activities, and is held under the auspices of the Turkish Authorities.

Table of contents

General information

EMEA Secretariat
7 Westferry Circus
London E14 4HB, UK
Tel.: + 44 (0) 20 74 18 85 18
Fax: + 44 (0) 20 74 18 85 01
E-mail: conferences@emea.europa.eu
Internet: http://www.emea.europa.eu/htms/euenlargement/croatiaturkey/index.htm

Registration desk
Opening hours:
Sunday: 16.00 - 18.00
Monday: 08.00 - 18.00
Tuesday: 08.00 - 18.00

The business centre level –2
Opening hours:
Monday: 08.00 – 18.30
Tuesday: 08.00 – 18.30
Tel.: + 90 212 631 12 12
Fax: + 90 212 631 37 02

Please ask the concierge for access

09.30 Welcome address

Chair: Thomas Lönngren, European Medicines Agency (EMEA)
Co-chairs: Orhan Fevzi Gümrükçüoğlu, Ministry of Health, *Turkey*
Nihat Pakdil, Ministry of Agriculture and Rural Affairs, *Turkey*

09.40 Keynote address

European Commission

Frédéric Misrahi, European Commission, Delegation in Turkey

Georgette Lalis, European Commission, DG Enterprise

Turkish Authorities

Erman Tuncel, Mayor of Istanbul, *Turkey*

Nihat Pakdil, Ministry of Agriculture and Rural Affairs, *Turkey*

Orhan Fevzi Gümrükçüoğlu, Ministry of Health, *Turkey*

10.30 - 11.00 Coffee break

11.00 Perspectives and challenges

11.00 **Turkish Ministry of Health's views**
Mahmut Tokaç, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

11.15 **Turkish Ministry of Agriculture and Rural Affairs' views**
Muzaffer Aydemir, General Directorate of Protection and Control, *Turkey*

11.30 **Responsibilities and mandate of National Competent Authorities as scientifically independent entities - Views of an established Member State**
Olga Apaligan, Federal Agency for Medicines and Health Products, *Belgium*

11.45 **Responsibilities and mandate of National Competent Authorities as scientifically independent entities - Views of a new Member State**
Tamás Paál, National Institute of Pharmacy, *Hungary*

Besides the European Medicines Agency, the importance of the National Competent Authorities and their collaboration to form a European medicines regulatory network is emphasised. Regulatory actions can be national (but subject of European procedures later), supranational (working in the regulatory network) and EU-wide ("on behalf of the Community"). Although the responsibilities of the National Competent Authorities may differ (covering only human medicines or also other products), there are general requirements. The key words characterising these are accountability, funding (that may differ from other governmental organs to answer the strict European soft- and hard-law deadlines), transparency and Good Regulatory Practices (e.g. operating a specific quality assurance system). To achieve that, the best organisational structure, not necessarily the same as operated before the accession, should be found. Hungarian examples will be presented.

12.00 **EMEA Structure and working principles**
Vincenzo Salvatore, EMEA

The first part of the presentation identifies the role and mission of the Agency as a European regulator for the market of medicinal products for human and veterinary use. This is followed by an illustration of the main principles that govern the relationship between the EMEA and, respectively, the European Commission and National Competent Authorities. A further part of the presentation is devoted to introducing the governing bodies of the Agency (i.e. the Executive Director and the Management Board) and to providing some basic information on the composition and functioning of the EMEA's scientific committees (CHMP, CVMP, COMP, HMPC, PDCO). Finally, some considerations are paid to the EMEA budget components and future priorities.

12.15 **EMEA Transparency policy**
Vincenzo Salvatore, EMEA

The presentation will focus on the commitment undertaken by the EMEA to provide all concerned stakeholders with prompt and accurate information on quality, safety and efficacy of medicinal products. Basic rules governing access to documents and requests for information are addressed in this presentation. Proactive vs reactive disclosure of information together with the need to find an equitable balance between the interest of transparency vis-à-vis the need to protect commercial confidential information are examined, highlighting the openness approach followed by the Agency and identifying the exceptions which might legally justify restrictions to information disclosure.

12.30 - 14.00 Lunch

14.00 Acquis communautaire: Perspectives for regulators

Chair: Eric Abadie, Chair of CHMP, French Health Products Safety Agency, *France*
Co-chair: Gabriel Beechinor, Irish Medicines Board, *Ireland*

- **The role of the Commission in the Regulatory System**
- **Centralised Procedure and Referrals**
- **Mutual Recognition Procedure and DCP**
- **Dossier upgrading & pre-EU-accession activities**
- **Compliance of products already on the market with EU Marketing Authorisation**

~

14.05 The role of the Commission in the Regulatory System
Matus Ferech, European Commission, DG Enterprise

14.20 **Centralised Procedure and Referrals**
Eric Abadie, Chair of CHMP, French Health Products Safety Agency, *France*

The European Medicines Agency (EMEA) started activities in London in 1995 giving Industry the opportunity to submit drug applications and get a marketing authorisation (MA) for the whole Union at once. The so-called "Centralised Procedure" is mandatory for all biotechnological products and for new entities targeting four disease areas: diabetes, cancer, HIV and neurodegenerative disorders. A Committee for Medicinal Products for Human Use (CHMP) evaluates the dossiers with the support of external experts during scientific discussions. The opinions of the CHMP to grant an MA are forwarded to the EU Commission, which takes the final decision. The EMEA and the CHMP have also the mandate to harmonise the information and the use of medicinal products across the Union.
Differences in medical and licensing practices are sometimes hardly acceptable for other National Competent Authorities. In case of divergences about the acceptability of a drug, the dispute can be referred to the CHMP for arbitration. Such referrals are discussed and a common European view sought to avoid disharmony in the Union. In more than a decade over 500 new chemical entities were licensed, reaching all countries in one go and remaining under the scrutiny of a single pharmacovigilance system strongly supported by the National Agencies active across the Union.

14.35 **Mutual Recognition Procedure and DCP**
Christa Wirthumer-Hoche, AGES PharmMed, *Austria*

The legal basis for the EU Registration Procedures is laid down in the European Pharmaceutical Legislation.

MRP: MRP will only be possible in cases where there exists already a marketing authorisation (MA). The Concerned Member State (CMS) shall recognise the MA granted by the Reference Member State (RMS). This existing MA in the RMS is the basis of an MRP. It is the decision of the experts in the CMS whether a further evaluation will take place during the 90-day European phase. In case all open questions are answered and clarified at day 90 of the MRP, all CMSs agree with the assessment report, the Summary of Product Characteristics (SPC), Package Leaflet (PL) and Label, the procedure can be finalised. The CMS will grant an MA within 30 days.

DCP: DCP can be chosen by an applicant if no MA is already existing in one of the EU-MSs. The procedure is divided into four steps:
First the pre-procedural step which starts 14 days before the start of the procedure.
During assessment step I the experts in the RMS will elaborate a preliminary assessment report (PrAR), which is the commented by the experts of the CMS. During a clock-stop procedure the applicant has to answer all the questions from RMS and CMS.
With the preparation of the Draft AR the RMS will restart the procedure, followed by the assessment step II for 90 days. In cases all the MS reaches an agreement the procedure can be finalised at any time point, at day 90 (210 days in total) at the latest.
During the national phase each MS (RMS and CMS) will grant a MA.

CMD-referral: As long as a CMS is raising serious risk to public health, the procedure (MRP/DCP) cannot be finalized, the issue has to be referred to the CMD (Coordination Group for MRP & DCP) for further scientific discussion within a 60-day procedure.

14.50 **Dossier upgrading & pre-EU-accession activities**
Rodica Badescu, National Medicines Agency, *Romania*

Upgrading of authorisation dossier for compliance with European standards
- ◊ Legal basis
- ◊ Purpose
- ◊ Characteristics of the process
- ◊ Timeline
- ◊ Results

Pre-EU-accession activities
- ◊ Transposition of the new pharmaceutical legislation
- ◊ Revision of translations for centrally authorised medicinal products
- ◊ Connection to the European IT system
- ◊ Organisational changes
- ◊ Staff training

15.05 **Compliance of products already on the market with EU Marketing Authorisation**
Rodica Badescu, National Medicines Agency, *Romania*

- ◊ Legal aspects
- ◊ Content and format of the marketing authorisation dossier
- ◊ EU GMP implementation and observance
- ◊ EU GCP implementation and observance
- ◊ Data exclusivity issues
- ◊ Medicinal products authorised through CADREAC/ n CADREAC procedures
- ◊ Special medicinal products:
  - Homeopathic medicinal products
  - Traditional herbal medicinal products
- ◊ Timelines for the implementation of provisions of the New Pharmaceutical Legislation

16.00 - 16.30 Coffee break

16. 30 Acquis communautaire: Challenges for industry

Chair: Kerstin Franzen, EFPIA
Co-Chair: Declan O'Brien, IFAH-Europe

- **Effect of a single market and availability of medicines**
- **Experience from an SME company**
- **Turkish views:**
  - ◊ **Pharmaceutical industry association**
  - ◊ **Research-based association**
  - ◊ **Association of Turkish Animal Health Industry**

~

16.35 Effect of a single market and availability of medicines

Hubertus Cranz, AESGP

The legislative and regulatory framework for non-prescription medicines has been strongly affected by the harmonisation process in the European Union since 1965. Today, the basic criteria for the classification of medicines into prescription/non-prescription, for public advertising and for supplying proof of safety and efficacy of well-established substances have all been harmonised. In parallel, there has been a growing recognition of the public health and economic value of responsible self-medication as the first choice of treatment in many illnesses.
The appropriate and consistent implementation of the European rules in the Member States nevertheless remains a challenge. Today there are still considerable differences in the availability of non-prescription medicines between the EU Member States. A key issue in this context is the possibility for manufacturers to freely set the prices of non-reimbursed medicines.

Greg Perry, EGA

The European generic medicines industry accounts for the vast majority of applications in the EU's DCP and MRP systems. The industry is also widening its applications to include the Centralised Procedure for both biosimilar and generic medicines. The presentation will review the impact of the current EU regulatory systems on the European generic medicines sector. It will also identify the contribution of generic and biosimilar medicines to the sustainability of European healthcare systems and the competitiveness of the European industry as a whole.

Kerstin Franzen, EFPIA

The legislative and regulatory framework for prescription & non-prescription medicines has been strongly affected by the harmonisation process in the European Union since 1965.
Today, the regulatory processes and the basic criteria, e.g. for the proof of safety and efficacy of drug substances, for determining the legal status of medicines, for advertising (to the Public and Health Professionals), for the content of the Summary of Product Characteristics are harmonised. The appropriate and consistent implementation of these rules in the Member States remains a challenge.

Such implementation should take into account the need for predictable timelines and scientifically reliable outcomes of regulatory processes, together with the growing desire of the people in Europe to be well informed and to take responsibility for their own health.

17.40 **Orphan Europe: Experience from an SME company**
Marie-Christine Fortun, Orphan Europe

Orphan Europe is an SME company totally dedicated to the development and the delivery of drugs for the treatment of rare diseases for more than 15 years.

An orphan disease is one that affects only very small numbers of individuals, most often neonates, children and young adults. They are usually severely debilitating or fatal since diagnosis is frequently difficult and delayed and often no definitive treatments exist.
Currently there are over 6,000 of these rare diseases which collectively means many millions are affected all over the word – well over 25 million in Europe alone.

An orphan disease is also often identified as one which has not been "adopted" by the pharmaceutical industry because it provides little financial incentive for them to make and market a new medicine to treat or prevent it.
The small numbers of sufferers with each disease mean the cost of research, licensing and marketing will never normally allow them to recoup their development costs.

Since 1990 Orphan Europe mission is to provide patients, healthcare personnel and the pharmaceutical industry with an independent global network, specializing in the development, registration, marketing and distribution of orphan medicinal products for the treatment of rare disorders.
The company currently has 10 products available and more in the pipeline.
Five of them are centrally approved in the 27 member states.
Indeed, for an SME, the centralised procedure is much easier to handle than the other European processes available for registration.

Having the EMEA as the single contact point (via the Product Team Leader) managing the evaluation done so far by the rapporteur and the co-rapporteur is very helpful.
Moreover, since the opening of the SME office at the EMEA, it is much easier to get answers to questions as quickly as possible.

Turkey's road to EU membership is very important from the patient healthcare point of view. Indeed once registered centrally, Turkish patients could have access to treatment as soon as the diagnosis is made.

17.50 **Turkish views**
Nurgün Örgen, Association of Research-based Pharmaceutical Companies, *Turkey*

AIFD, which represents the research-based pharmaceutical industry in Turkey, supports the EMEA multi-beneficiary program on participation of Turkey.
Although many regulations have been successfully revised during the recent past, there are still certain areas to focus either to revise or to improve revised regulations in terms of implementation. The presentation outlines the key areas where beneficial changes might be made and suggests a way in which high priority areas could be expedited from pharmaceutical industry perspective.
Some of the key areas to be focused are: registration timeline, impact of market access delays on IPR, new regulation need for improvement of approval timelines & standardisation for clinical trials, lack of complete OTC regulation, etc.

Murat Salihoglu, Pharmaceutical Manufacturers Association, *Turkey*

- Brief about Pharmaceutical Manufacturers Association of Turkey
- Facts and Figures about Turkish Market– 2006
- The Pharmaceutical Market in Turkey
- Regulatory Environment
- Establishment of Medicines & Medical Devices Agency and expectations
- Conclusions & Comments

Burhan Haci, Association of Turkish Animal Health Industry, *Turkey*

VISAD, Association of Turkish Animal Health Industry is a non-profit industry organisation established in 1991, representing manufacturers and importers of veterinary medicines, vaccines and other animal health products in Turkey. VISAD member companies consist of 75% of the Turkish market for veterinary pharmaceutical products.

VISAD acts as the voice of the industry in dialogue with the State bodies (MARA, Institutes, Universities and others); encourages and assists the development and implementation of regulatory processes and standards which are aligned with EU; represents the industry with a unified, global voice in dealings with governments, food industry partners and consumers.

With its high number of food-producing animals, the Turkish animal health market is sizeable and expected to grow at around 7-8% p.a. However, there is a certain need for establishing and improving the basic regulations and controls in regard to registration, manufacturing, sales and usage of veterinary pharmaceuticals in the market.

With the changing structure of animal production and the projected increases in consumption of animal-origin foods, the need for a better-regulated animal-health sector is becoming essential. Harmonisation with EU norms and standards in respect of legislation for veterinary products and animal-health policy will be expedient to overcome many difficulties experienced in animal and public health in Turkey.

~

20.00 Welcome reception

21.00 Conference dinner

Venue

Ziyafet Divan
Kuruçesme Caddesi 61,
34345 Kuruçesme - Istanbul

Tel: +90 212 257 71 50.

Transfer

Transfer from the Hotel Barceló to the Ziyafet Divan will be provided to the guests (speakers and delegates) invited by the EMEA only.

The meeting point will be in the lobby of the hotel Barceló between 19.00 and 19.30.
The return transfer to the hotel Barceló will be from 22.30 to 23.00.

09.00 Session I: Access to medicines

Chair: Melanie Carr, EMEA
Co-chair: Fahri Ovali, Zeynep Kamil Research Hospital
Eda Cindoğlu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

- **Biosimilars: Guidelines and current experience**
- **Incentives for:**
  - ◊ **Orphan drugs**
  - ◊ **Paediatric medicines**
  - ◊ **SMEs**

~

09.05 Biosimilars: Guidelines and current experience

Peter Richardson, EMEA

The EMEA has the task to develop the scientific requirements for Marketing Authorisations for biosimilar products, and a number of guidelines have recently been prepared to achieve this. Other guidance is being developed.

For biosimilar products, a full quality-data package is required. The elements of the dossier which may be abridged are the non-clinical and clinical data and the biosimilar product is compared versus an EU authorised reference product.

To date, two biosimilar products have been authorised: Omnitrope and Valtropin, which both contain somatropin, and in June 2007 the CHMP gave positive opinions for three epoetin alfa biosimilar products. Other regions are debating the introduction of biosimilars, as they have been termed in the EU (and also in the USA), and interest in this class of products continues to grow.

09.20 Incentives for orphan drugs, paediatric medicines and SMEs

Melanie Carr, EMEA

In 2000, EU 'orphan' legislation introduced incentives to stimulate research into and the development of medicinal products for rare diseases. Provisions to facilitate the regulatory process for pharmaceutical companies fulfilling the definition of a micro, small and medium-sized enterprise (SME) were implemented in 2005. Most recently, legislation entered into force in the EU that will dramatically modify the way medicines are developed for children, with a view to increasing research into, information on, and availability of medicines.

The presentation will provide a brief overview of the various initiatives designed to promote innovation and the development of new medicinal products at EU level.

09.00 Session II: Safety of veterinary medicines

Chair: Gabriel Beechinor, Irish Medicines Board, *Ireland*
Co-chair: Recai Kandur, Head of Veterinary Medicinal Tasks Subsection, *Turkey*

- **MRLs and consumer safety**
- **Environmental risk assessment, user safety and antimicrobial resistance**
- **EU veterinary pharmacovigilance-specific issues**

~

09.05 MRLs and consumer safety

Jos Olaerts, EMEA

Consumer safety is one of the main aspects considered with regard to the safety of veterinary medicines. The most important aspect in order to protect the health of the consumer with regard to foodstuffs of animal origin is to ensure that foodstuffs obtained from animals treated with veterinary medicinal products do not contain residues of the medicine that might constitute a health hazard to the consumer. This presentation will address the regulatory requirements for the establishment of maximum residue limits (MRLs) and withdrawal periods in the European Union, and summarise the procedure and approach for the scientific evaluation.

09.20 Environmental risk assessment, user safety and antimicrobial resistance

Gabriel Beechinor, Irish Medicines Board, *Ireland*

An environmental risk assessment (ERA) is required for all new veterinary medicines, including generics. ERAs should follow EU guidelines using a step-wise, phased approach. In phase I, the potential environmental exposure is estimated based on the intended use of the product. Medicines with limited environmental exposure stop at this phase. The phase II guidance considers specific advice in respect of medicines for aquaculture, intensively reared terrestrial animals and pasture animals using a two-tiered approach - the first makes use of simpler studies (physical/chemical properties, environmental fate) to estimate risk based on exposure and effects in the environmental compartment of concern. Where the ERA cannot be completed with such data, the second tier (more exhaustive data) is triggered. In some cases, it may be possible to implement a risk management option instead of moving to the second tier. From 1 November 2007, additional, more specific technical advice comes into effect in the European Economic Area. This guideline provides regional regulatory guidance on those points on which the existing VICH guidelines are more general.

The assessment of the risk that may result from the exposure of humans (including professional and non-professional users) to a veterinary medicine, e.g. during administration, is an intrinsic part of the safety assessment. The assessment follows the standard risk assessment steps and involves the consideration of all relevant exposure scenarios and the characterisation of risks for each scenario. The hazards are identified on the basis of appropriate toxicology tests, including relevant endpoints for local and systemic toxicity and taking into account the route, duration and frequency of exposure. Where there is a predicted risk for the user, appropriate measures for risk reduction are evaluated. Any precautions for use identified must be stated in the Summary of Product Characteristics and package leaflet.

Antimicrobial resistance is an important and long-standing area of interest in the European Union. All new antimicrobial substances intended for use in food-producing animals must provide pre-approval data to characterise the potential to select for resistant bacteria of human health concern.

Programme overview

Monday 22 October 2007

	Ballroom
09.30 - 10.45	**Welcome address and keynote address**
10.35 - 11.15	**Coffee break**
11.15 - 12.30	**Perspectives and challenges**
12.30 - 14.00	**Lunch**
14.00 - 16.00	**Acquis communautaire:** Perspectives for regulators
16.00 - 16.30	**Coffee break**
16.30 - 18.30	**Acquis communautaire:** Challenges for industry
20.00 - 21.00	**Welcome reception**
21.00 - 23.00	**Conference dinner**

* Simultaneous interpretation in English and Turkish

Tuesday 23 October 2007

	Ballroom	Mallorca
09.00 - 10.00	**Session I: Access to medicines** • Biosimilars: Guidelines and current experience • Incentives for orphan drugs, paediatric medicines and SMEs	**Session II: Safety of veterinary medicines** • MRLs and consumer safety • Environmental risk assessment, user safety and antimicrobial resistance • EU veterinary pharmacovigilance-specific issues
10.00 - 10.30	**Coffee break**	
10.30 - 12.00	**Session III: Specific regulatory issues** • Borderline products, legislation, implementation • Clarification on traditional herbal products, and fast-track registration process • Classification issues and possible switch to OTC • Licensing of borderline products	**Session IV: Authorisation of veterinary medicines** • Effect of a single market and availability of veterinary medicines • Challenges for veterinary generics • Immunologicals • Genetically modified organisms (GMOs) • Quality of veterinary medicines
12.00 - 13.30	**Lunch**	
13.30 - 15.30	**Session V: Pharmacovigilance** • Outline of the EU pharmacovigilance system • EudraVigilance and risk management within the EU pharmacovigilance system • Technical aspects of EudraVigilance • Pharmacovigilance system in Turkey	**Session VI: GCP inspections and related activities** • Clinical trials and GCP inspections findings • Ethics committees • Implementation of GLP principles in the EU • GLP inspection system and findings • GCP in Turkey
15.30 - 16.00	**Coffee break**	
16.00 - 18.00	**GMP inspection and related activities** • GMP inspections in Turkey • GMP inspection system in the EEA EudraGMP • Role of the qualified person • Rapid alert procedure and product defects • Anti-counterfeit initiatives • Medicinal gases	
18.00 - 18.15	**Close**	

* Simultaneous interpretation in English and Turkish

09.35 **EU veterinary pharmacovigilance-specific issues**
Jos Olaerts, EMEA

Pharmacovigilance for veterinary medicinal products (VMPs) is increasingly in the spotlight since further emphasis was put on post-marketing surveillance instead of renewal procedures of marketing authorisations, and the implementation of the central EU database for exchange of veterinary pharmacovigilance information: EudraVigilance Veterinary. This presentation provides an overview of the pharmacovigilance obligations for marketing authorisation holders and competent authorities in the EU concerning VMPs and the status of the current shift towards electronic reporting of veterinary pharmacovigilance information. It seeks to explain the basic principles, structures and procedures that are in place in the EU for the exchange of veterinary pharmacovigilance information for VMPs for all stakeholders—competent authorities as well as industry partners—to better understand their role in the development of pharmacovigilance surveillance of VMPs in the EU.

10.00 - 10.30 Coffee break

10.30 Session III: Specific regulatory issues

Chair: Zaide Frias, EMEA
Co-chair: Ahmet Basaran, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*
Hulya Karahasanoglu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*
Hubertus Cranz, AESGP

- **Borderline products, legislation, implementation**
- **Clarification on traditional herbal products, and fast-track registration process**
- **Classification issues and possible switch to OTC**

~

10.35 Borderline products, legislation, implementation
Hubertus Cranz, AESGP

Medicinal products are defined by Directive 2001/83/EC (as amended) as substances presented as having properties for treating or preventing disease or which may be administered to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action. This definition may lead to a certain degree of uncertainty when drawing the borderline between medicinal products and other categories of products which are defined and regulated at the European level by other pieces of Community legislation, e.g. medical devices, cosmetics, fortified foods and food supplements. With regard to the latter, the health claim regulation and the setting of harmonised maximum levels for vitamins and minerals may create more clarity in this borderline area and would be an important step further in the harmonisation process. So far, Member State authorities are primarily responsible for determining the nature of a product on the basis of a case-by-case analysis.

11.00 Clarification on traditional herbal products, and fast-track registration process
Lucia D'Apote, EMEA

The presentation will provide an overall summary of the legislative framework for traditional herbal medicinal products (THMPs) and will outline the opportunities offered by the new legislation to register traditional and modern herbal medicinal products. In addition, the participants will be informed about the role of the Committee on Herbal Medicinal Products (HMPC) and its recent achievements working towards facilitating the access to the European market.

11.25 Classification issues and possible switch to OTC
Zaide Frias, EMEA

The criteria for classifying medicines as prescription and non-prescription were harmonised in the European Union in the early 1990s. Many medicinal products have been moved from prescription to non-prescription status since that time. However, there are still considerable differences between the EU Member States due to divergent attitudes towards self-medication. In parallel, the range of indications acceptable for self-medication expanded.
The revised pharmaceutical legislation adopted in 2004 established a data-exclusivity period of one year for relevant scientific work in the context of the move from prescription to non-prescription status. Details were laid down in the updated guideline of the European Commission on the change of classification status. All this became a topic of direct importance for the EMEA in light of the opening of the centralised procedure for innovative non-prescription medicines.

11.50 **Licensing of borderline products**

Hülya Karahasanoğlu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

There is no specific herbal medicinal products registration procedure in Turkey at the moment. Medicinal products which contain herbal ingredients are registered as human medicinal products.

Just like nutraceuticals that are categorised as medicinal products there are a group of products which are considered as treatment supporters and are called borderline products in Turkey.

Licensing Regulation of the Human Medicinal Products had been published at Official Gazette 25705 on the 19th of January 2005. According to its provisional article 2, until a new regulation on this subject is prepared "Borderline Guideline" which was in force since 1999 depending on the previous licensing regulation's article 39 is in force.

The borderline dossier should be in separated divisions and in Standard file format. If the information given in dossier is in foreign languages the Turkish translation and reference's details are required by the related Department.

The dossier has to include information about the active ingredients, analysis control, production method, stability studies for the finished product, package usage in detail. The applicant is not supposed to submit pharmacological and toxicological study results.

These products are not considered as medicinal product so should not have any indication stated on the package and usage leaflet.

10.30 Session IV: Authorisation of veterinary medicinal products

Chair: Jill Ashley-Smith, EMEA
Co-chair: Muzaffer Aydemir, General Directorate of Protection and Control, *Turkey*

- **Effect of a single market and availability of veterinary medicines**
- **Challenges for veterinary generics**
- **Immunologicals**
- **Genetically modified organisms (GMOs)**
- **Quality of veterinary medicines**

~

10.35 Effect of a single market and availability of veterinary medicines
Christian Van Beek, IFAH-Europe / Intervet

The presentation will deal with the industry view on EU enlargements and will cover the following elements:

- the need for good cooperation between both authorities and veterinary industry as they share a common goal to "safeguard animal health and welfare as well as public health";
- lessons learned from previous EU enlargements;
- will indicate (possible) problem areas (packaging material issue; review procedure);
- give advice to new EU member states (gaining experience - participation in MRP/ DCPs from the sideline prior to EU accession and the need to be practical).

10.50 Challenges for veterinary generics
Rob Joosten, EGGVP

In the Directive 2004/28/EC article 13 has been modified to a large extend as compared to the previous version. This modification gives certainly wider possibilities for applications for generics. Besides these new opportunities and challenges it now also appears that threats can be a result of the new provisions.

An applicant's view on:

- informed consent applications;
- bibliographic applications;
- applications based on essential similarity.

11.05 Immunologicals
Tibor Soós, Directorate of Veterinary Medicinal Products, *Hungary*

The presentation gives a short summary about the experiences Hungary had while joining the European Union. On the basis of statistical data, it analyses the effects of the joining on the Hungarian animal health industry and the National Competent Authority. When presenting the effects of the EU-joining it also pays attention to the experiences of other countries, which had become member states in 2004. It outlines the strategy followed by the National Competent Authority during the pre-accession period. It emphasises the importance of the pre-joining voluntary harmonisation. It draws attention to the close cooperation between the industry and the Competent Authority during the preparations.

It reminds of the most important instructions and guidelines relating to the authorisation and control of immunobiological products.

11.20 **Genetically modified organisms (GMOs)**
Jill Ashley-Smith, EMEA

The presentation will give a short overview of the Centralised Procedure, highlighting the additional steps required for a product which consists of or contains a GMO. Focus will be placed on the definition of a GMO, the legal basis for these applications, how the EMEA processes the applications and how the EMEA involves the Competent Authorities of the European Economic Area in the evaluation of these products.

Information will also be provided on the role of the various bodies in the approval of these products and the implications for Accession Countries. Lastly, the availability of guidance for applicants and regulators will be highlighted.

11.30 **Qualitiy of veterinary medicines**
Teresa Potter, EMEA

This presentation will focus on the quality of non-immunological veterinary medicinal products. It will include an introduction to the Quality Working Party (QWP) and its work, and will touch on other Committees/Working Parties with which the QWP interacts.

Information will then be provided on the range of veterinary quality guidance documents (from both the EU and VICH), including a summary of how such guidance is developed. Some current topical quality issues will be highlighted.

Lastly, for the benefit of both applicants and regulators, detail will also be included on where such guidance can be found.

12.00 - 13.30 Lunch

13.30 Session V: Pharmacovigilance

Chair: François Maignen, EMEA
Co-chair: Demet Aydinkarahaliloglu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

- **Outline of the EU pharmacovigilance system**
- **EudraVigilance and risk management within the EU pharmacovigilance system**
- **Technical aspects of EudraVigilance**
- **Pharmacovigilance system in Turkey**

~

13.35 Outline of the EU pharmacovigilance system

François Maignen, EMEA

This session will provide a picture of the current functioning of the EU pharmacovigilance system. The interaction between all involved parties will be described for all medicinal products, irrespective of the licensing route. Furthermore, emphasis will be put on the initiatives undertaken to further strengthen the EU pharmacovigilance system.

14.00 EudraVigilance and risk management within the EU pharmacovigilance system

François Maignen, EMEA

In this respect the European Risk Management Strategy (ERMS) will be discussed, in particular as regards the current status and the next steps.

14.25 Technical aspects of EudraVigilance

Hans-Georg Wagner, EMEA

The information system supporting pharmacovigilance in the EEA, EudraVigilance, is a complicated IT system. This presentation decribes its IT architecture, and how it fits within the family of EU Telematics applications. It goes on to discuss implementation options for sponsors, marketing-authorisation holders and regulators.

14.50 **Pharmacovigilance system in Turkey**

Demet Aydinkarahaliloglu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

The '**Regulation on the Monitorization and Assessment of the Safety of Medicinal Products for Human Use**' has been prepared in accordance with EC directive 2001/83/EC and Pharmacovigilance Guideline, Volume 9. It has been published in the Official Gazette and has become effective along with '**Pharmacovigilance Guideline for Marketing Authorization Holders of Medicinal Products for Human Use**' on June 30, 2005.

Along with the Guideline, the name of the Turkish Center for Monitoring and Evaluation of Adverse Drug Reactions (TADMER) which was founded in 1985 within the Department of Quality Control, General Directorate of Pharmaceuticals and Pharmacy had become a member of the WHO Collaborating Centre for International Drug Monitoring in 1987 has been changed as TUFAM (Turkish Pharmacovigilance Center).

In the Guideline, the responsibilities of the parties involved and the monitoring of adverse drug reactions, the reporting to be done and the evaluation of these reports within these responsibilities have been clarified and it has been emphasised that it is the professional responsibility of the health professionals to report adverse drug reactions to the Ministry of Health.

The health professionals that can report adverse drug reactions to TUFAM include doctors, pharmacists, dentists and nurses. The system is based on the assignment of a pharmacist or a doctor as the contact point in university hospitals, training and research hospitals and group A-1 private hospitals instead of forming regional pharmacovigilance centers. To provide scientific advice on drug safety issues, an **Advisory Committee for Monitorization and Assessment of Safety of Medicinal Products for Human Use** has been formed within the General Directorate of Pharmaceuticals and Pharmacy. The committee has 12 members.

Among the main data sources of TUFAM are spontaneous adverse drug reaction reports, literature dependent adverse reaction reports and PSURs. In addition, developments in the area of drug safety is being followed up worldwide, regularly.

In the adverse drug reaction reports made spontaneously to TUFAM, adverse drug reaction(s) is classified according to WHO-ART terminology, the diseases are coded according to ICD-10 and sent to WHO-UMC via Vigiflow.

Finally, training meetings are being organized by TUFAM for Drug Safety Officers that are appointed by marketing-authorisation holders and for pharmacovigilance contact points.

13.30 Session VI: GCP inspections and related activities

Chair: David Cockbrun, EMEA
Co-chair: Berna Terzioglu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

- **Clinical trials and GCP inspections findings**
- **Ethics committees**
- **Implementation of GLP principles in the EU**
- **GLP inspection system and findings**
- **Clinical trials in Turkey**

~

13.35 Clinical trials and GCP inspections findings

Adina Pirvu, National Medicines Agency, *Romania*

- Transposition of European Clinical Trials legislation into Romanian legislation
- Regulatory framework for clinical trials in Romania
  Minister of Health Orders (MHO) transposing Clinical Trials Directives
  National Medicines Agency Scientific Council Decisions approving translation into Romanian of guidelines included in volume 10 – Clinical trials of the Rules governing medicinal products in the European Union
- Clinical trials and GCP inspections in Romania
  - ◊ Approval of clinical trials in Romania
    - Number of clinical trials conducted in Romania in 2006
  - ◊ 3.2. Performance of GCP inspections in Romania
    - Organisation of the GCP Inspection Compartment
    - GCP inspection procedures
    - Stages of GCP inspection
    - Triggers for selection of the trial/ site to be inspected
    - Number of GCP inspections conducted in Romania in 2006
- GCP inspection findings
  - ◊ Classification of inspection findings
  - ◊ Example of deficiencies identified in inspection reports

14.00 Ethics committees

Mats Ericson, Wyeth Pharmaceuticals, *France*

14.35 Implementation of GLP principles in the EU

Rob Jaspers, Food and Consumer Products Safety Authority, *The Netherlands*

The development of the OECD principles of GLP and the adoption of the principles by EU member states will be discussed in this presentation. The GLP principles have to be followed when conducting certain types of studies including (eco)toxicity and mutagenicity studies. The test results are used for registration and approval of various types of chemicals, such as pharmaceuticals and pesticides. EU member states have established national GLP-compliance-monitoring authorities to monitor the implementation and correct use of the principles. Representatives of these agencies meet on a regular basis in the EU Working Group on GLP. To inform all member states, each monitoring authority prepares annually an overview of its inspection results. Members of the Working Group can access this information on a password-protected website of the European Commission.

Information on GLP, including references to European legislation can be found on the following website of the Commission:
http://ec.europa.eu/enterprise/chemicals/legislation/glp/index_en.htm.

14.55 GLP inspection system and findings

Andrew Gray, Medicines and Healthcare products Regulatory Agency, *UK*

Good Laboratory Practice (GLP) inspections are generally performed as part of a routine inspection programme but are also conducted as a result of concerns raised by receiving authorities who assess pre-clinical data. The primary purpose of the inspection process is to ensure that test facilities adhere to the principles of GLP which in turn ensures the proper planning of studies and the provision of adequate means to carry them out. The implementation of key GLP systems facilitates the proper conduct of studies, promotes their full and accurate reporting and provides a means whereby the validity and integrity of the study can be verified. This presentation will outline the various approaches taken when conducting GLP inspections, including the conduct of GLP study audits requested by receiving authorities. The presentation will discuss the classification of deficiencies and identify areas of GLP compliance which continue to cause issues; these will include the conduct of multi-site studies, computer validation and quality-assurance monitoring.

15.15 Clinical trials in Turkey

Berna Terzioğlu, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

Turkey is in the review phase to join the European Union (EU) and has undergone many important reforms involving patients' rights, criminal law, and specialised biotech drug dispending acts and so on.

Turkey was formally accepted as a candidate for EU membership in December 2004. This is crucial step in Turkey's long campaign to become part of the European Community. Along with policies and visions for scientific and technological development put forward by EU in the mid 1990s. Turkey has taken major steps toward harmonising with the EU in the field of clinical research and drug trials.

Turkey was expected to implement the Regulations for Clinical Research and Regional Ethics Committees on Human Medicinal Products at the end of this year. This new legislation effectively meets EU Directive 2001/20/EC and 2005/83/EC requirements for conducting clinical trials.
The regulation of clinical trials in Turkey is relatively recent, dating back to 1993, when the Regulation Relating to Drug Research was introduced. Two years later, Directorate of Drug and Pharmacy published GCP (Good Clinical Practice) and GLP (Good Laboratory Practice) Guidelines.

This GCP Guideline covers all the essential rules and regulations for clinical trials to be conducted on human subjects, procedures for obtaining informed consent and constitution and activities of ethics committees. Its primary aim was to protect all aspects of participants' well-being and to guarantee the accuracy and robustness of the data obtained. It was also intended to ensure that the data was collected in compliance with ethical standards.

This regulation established a two-tier system for the ethical oversight of clinical trials. Protocols first had to be approved by the institution's own local ethics committee (LEC), and then submitted for approval by a central ethics committee (CEC) within the Ministry of Health (MoH). So, approval letter is given by MoH for the start of the clinical trials.
There are now 82 LECs. According to the regulation, LECs had to comprise at least seven members.

The new legislation has a number of objectives: to speed up approval procedures, to motivate investigators, and to track the whole procedure precisely, all of which are essential perquisites if Turkey is to realise its potential as a location for clinical studies. It should also ensure greater accuracy and reliability of the data collected in the clinical setting.

15.30 - 16.00 Coffee break

16.00 GMP inspections and related activities

Chair: Katrin Nodop, EMEA
Co-chair: Fatma Bekar, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

- **GMP inspections in Turkey**
- **GMP inspection system in the EEA**
  - ◊ **EudraGMP**
  - ◊ **Role of the qualified person**
  - ◊ **Training and qualification of inspectors**
- **Rapid alert procedure and product defects**
- **Anti-counterfeit initiatives**
- **Special topic: Medical gases**

~

16.05 **GMP inspections in Turkey**
Fatma Bekar, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*

The inspections of the pharmaceutical manufacturers and medical gas manufacturers are carried by GD's Quality Control Department according to the GMP Directives and Guidelines once a year. The inspections are in the responsibility of the Ministry of Health inspectors with the cooperation of GD and National Hygiene Institute representatives.

If the pharmaceutical products are imported from non-PIC member states and haven't any FDA, EMEA, PIC GMP certificate the related Department requires GMP inspection.

The market surveillance of the medicinal products is carried by the Quality Control Department of the GD which includes product sampling and analysis at the National Drug Control Laboratory.

The export certificates issued by our GD are; GMP Certificate of Manufacturers, GMP and Free Sales Certificate of Pharmaceuticals, Certificate of Pharmaceutical Product.

16.25 **GMP inspection system in the EEA EudraGMP**
Katrin Nodop, EMEA

GMP inspections are a critical part of the regulatory framework that ensures that medicinal products are appropriately manufactured and adhere to the standards of quality defined in the marketing authorisation. The presentation will describe how these inspections are organised in the EEA. It will explain roles and responsibilities at national and Community level and introduces the EudraGMP database.

16.45 **Role of the qualified person. Training and qualification**
David Cockburn, EMEA

The role of the qualified person is fundamental to the EU system. The qualified person must fulfil specific legal obligations prior to the release of medicinal products onto the European Community market. Practical issues will be discussed including what the qualified person is allowed to do and not allowed to do. The second part of the presentation is focussed on inspectors. Each Member State has a duty to the rest of the European Community to supervise the manufacture of medicinal products within its territory and is therefore required to have suitably qualified and trained GMP inspectors. How this is achieved is outlined.

17.05 **Rapid alert procedure and product defects**
Anti-counterfeit initiatives
Katrin Nodop, EMEA

In order to protect public health and animal health, it may become necessary to recall defective batches of a medicinal product from the market. Counterfeit medicinal products undermine the regulatory system which assures patients of safe and efficacious medicines. The presentation will explain the Community procedures for handling quality defects and what is going on in the fight against counterfeit medicines.

17.25 **Medicinal gases – Expectations and experiences during GMP inspection in Germany**
Christa Färber, Trade and Industrial Inspection Agency of the State of Lower Saxony - Agency Hannover, Germany

Manufacturing of active substances is subject to the requirements of Part II of the EU GMP Guide, whereas the production of bulk medicinal product - normally defined as first storage for pharmaceutical purpose - has to fulfil the requirements of Part I of the Guide. Specific requirements are part of the Annex 6, actually in revision.
Companies have to define clearly the delineation between active substance and bulk medicinal product in agreement with the national competent authorities.
Main focus during inspection should be put on the following items:

- Qualification of equipment
- Process validation
- Handling and filling of cylinders/mobile cryogenic vessels (particularly in regard to fill empty cylinders)
- Process of release and time of release incl. documentation

Most GMP problems detected during inspection are "handling of empty cylinders" and "filling of empty cylinders without visual inspection" not least "documentation and release".

18.00 Close of the conference

Chair: Sylvie Bénéfice, EMEA
Co-chair: Mahmut Tokaç, General Directorate of Pharmaceuticals and Pharmacy, *Turkey*
Muzaffer Aydemir, General Directorate of Protection and Control, *Turkey*

Glossary

AESGP	Association of the European Self-Medication Industry
AFSSAPS	French Health Products Safety Agency
CHMP	Committee for Medicinal Products for Human Use
CVMP	Committee for Medicinal Products for Veterinary Use
COMP	Committee for Orphan Medicinal Products
EGA	European Generic Medicines Association
EGGVP	European Group for Generic Veterinary Products
EFPIA	European Federation of Pharmaceutical Industry Associations
EMEA	European Medicines Agency
FAGG	Federal Agency for Medicines and Health Products
IFAH	International Federation for Animal Health

We look forward to meeting you again.