

# Guiding Principles on Self-Medication

### *Chairpersons:*

- *Mr Patrick Deboyser, Head of Unit, Pharmaceuticals and Cosmetics, European Commission*
- *Dr Michael Scholtz, Executive Director for Health Technology and Pharmaceuticals, World Health Organization (WHO)*

### **DEBOYSER:**

*I am pleased to welcome you at the Regulators' Forum at this joint WSMI/AESGP meeting in Berlin. My name is Patrick DEBOYSER and am currently (for another few days) Head of the Pharmaceuticals and Cosmetics Unit at the European Commission in Brussels. In fact, I will move to the Foodstuffs Unit next week, on 15 June 1999. My co-chair for this morning's session is DR MICHAEL SCHOLTZ, Executive Director for Health Technology and Pharmaceuticals in the World Health Organization (WHO) since July 1998. Prior to this, Dr Scholtz had various positions in the pharmaceutical industry, mainly focused on marketing and strategic planning. Other participants around the table are (as introduced by themselves):*

- **Alfred JOST**, Deputy Director of the Swiss Regulatory Authority with responsibility for the Legal and Information Department. Mr Jost said he was particularly interested in participating because Switzerland, although not an EU member, is surrounded by EU Member States. Switzerland has the languages of its neighbours (German, French and Italian) and is right in the middle of globalisation. It can learn a lot from the issues discussed at the conference.
- **June RAINE** from Medicines Control Agency (MCA), London, UK, with responsibility for post-authorisation issues for medicines, including switching from prescription to OTC, product information and advertising.
- **LE Van Truyen** from Vietnam, Vice-Minister of Health, in charge of traditional medicines, medical and pharmaceutical legislation and pharmaceuticals. Professor Le has been teaching for 20 years in the Faculty of Pharmacy of Hanoi. For 10 years he was a Director of a pharmaceutical factory and also spent 10 years in the Ministry of Health. Professor Le said he had especially come to learn as he was one of the few representatives from Southeast Asia present at the conference.
- **Lembit RÄGO**, Director General of the State Agency of Medicines, Estonia.
- **Milan ŠMÍD**, Director, State Institute for Drug Control, Czech Republic.
- **José CAMPILLO**, Under Secretary of Health, Mexico, responsible for regulation of health services, products, exports, imports, etc.
- **Tom MCGUINN**, Chief Pharmacist in the Ministry of Health, Ireland, involved in the control of medicinal products on the one side and in reimbursement strategies and policies on the other side.

- **Jasmina MIRCHEVA**, AESGP's Director for Medicinal Affairs and Central & Eastern Europe, has a scientific background and spent 20 years teaching at universities. In 1995, Professor Mircheva was appointed Director of the State Institute for Drug Control, Bulgaria. She joined AESGP in June 1998.
- **Bernd EBERWEIN**, Director of the German Medicines Manufacturers' Association (BAH) based in Bonn and Berlin.
- **Geeta LINGAM**, Head of International OTC Regulatory Affairs, Glaxo Wellcome, based in the UK.
- **Ralf MÜLLER**, currently AESGP's Director for Strategic Projects, was previously Marketing Manager, Bayer, Germany, responsible for analgesics and cough & cold products.
- **Flavio VORMITTAG**, Medical Director of Whitehall, Medical Director of the Brazilian Self-medication Industry Association and President of the Brazilian Association of Pharmaceutical Physicians, Brazil.
- **Gonzalo VECINA NETO**, Head of the National Regulatory Agency, Brazil, responsible for all regulatory matters concerning medicines, food, cosmetics and medical devices.
- **Victor DIMITRIEV**, Deputy Director of the Research Centre for Drugs Evaluation and State Control, Russian Federation.
- **Elena BARMANOVA**, Research Centre for Drugs Evaluation and State Control, Russian Federation, with responsibility for regulatory affairs for OTC products.
- **Elena VOLSKAYA**, Research Centre for Drugs Evaluation and State Control, Russian Federation. Mrs Volskaya is responsible for pharmaceutical advertising.
- **Alexander RUDAKOV**, Director, National Institute for Preclinical and Clinical Drug Evaluation, Russian Federation. Professor Rudakov is also Deputy Director of the Pharmacological Committee. The Pharmacological Committee and the Institute are responsible for the expertise and the documentation of all new medicines proposed for registration in Russia as well as for clinical trials.
- **Vladas VOLBEKAS**, Chairman of the Drug Registration Commission, State Medicines Control Agency, Lithuania
- **L'udevít MARTINEC**, Director, State Institute for the Control of Drugs, Slovak Republic
- **Aleksander MAZUREK**, Director, Drug Institute and Chairman, Drug Registration Committee, Poland
- **Tomasz KRASUCKI**, Chairman, Bureau of Registration of Drugs and Medical Devices, Drug Institute, Poland
- **Tamás PAÁL**, Director-General, National Institute of Pharmacy, Hungary and Head, Department of Pharmacy, "Haynal Imre" University of Health Sciences, Budapest. Professor Paál has a scientific, industrial and regulatory background. He has been heading the Hungarian drug regulatory agency for 15 years.
- **Gonzalo NAVARRETE**, Director, Institute of Public Health, Chile. The Institute is responsible for regulatory affairs aspects of all medicinal products.
- **Graham PEACHEY**, Therapeutic Goods Administration (TGA), Australia. Mr. Peachey is Director of the TGA's chemical and non-prescription medicines branch. He has been with the TGA since September 1998. Prior to that, Mr Peachey was General Manager of the Australia-New Zealand Food Authority.
- **Alfred HILDEBRANDT**, Director, Institute for Medicines and Medical Devices (BfArM), Germany. Professor Hildebrandt is a member of the Committee for Proprietary Medicinal Products (CPMP) at the EMEA in London and Chairperson of the CPMP Efficacy Working Party.
- **Murray LUMPKIN**, Deputy Center Director (Review Management), Center for Drug Evaluation & Research, Food and Drug Administration (FDA), USA. Dr Lumpkin is responsible for the pre-marketing and post-marketing oversight programme for prescription and OTC medicines in the USA.

#### DEBOYSER:

It is perhaps appropriate that we meet in the very room in which took place the 9th meeting of the International Conference of Drug Regulatory Authorities (ICDRA) six weeks ago, a meeting which was also addressed by WHO's Dr Gro Harlem Brundtland.

This morning we have again gathered a number of regulators from across the world who will, together with some self-medication industry representatives, discuss the main reference document for this session, the World Self-Medication Industry's "Guiding Principles on Self-Medication". There will be no attempt this morning to draw any conclusions or to make statements. We will mainly discuss ideas and exchange views. We may per-

haps come to some consensus views, but we will not try to consolidate these into a statement or a joint conclusion.

Michael and I are proposing to organise this forum in a way that in the first half of the meeting we will look particularly at the following issues:

- marketing authorisation / marketing approval for self-medication products
- classification of products into prescription-only and non-prescription (OTC) medicines
- switching from prescription-only to non-prescription status

In the second half of the morning, we will concentrate on issues such as

- promotion / advertising of self-medication products
- brand names / umbrella brands, etc.

Those sitting at the table with a microphone are basically the regulators and some industry representatives. However, the so-called "backbenchers" can also participate in the debate by asking questions.

Concerning the WSMI's "Guiding Principles on Self-Medication", we will not look at the first two chapters as these have already been dealt with extensively at the main part of the conference. Rather, we will concentrate on some of the more topical subjects starting with chapter 3 ("The Classification of Medicines") which deals with issues such as marketing authorisation, classification, expedited authorisation and traditional medicines. We will first hear a presentation by Prof. Martinec from Slovakia.

## **MARTINEC:**

### **Introduction**

Legislation and regulation constitute important elements in any drug policy. The legal framework must take into account not only policy objectives but also the administration, social and health infrastructure, the available manpower and other resources.

Drug legislation and regulation address the rights and responsibilities of the different parties concerned with drugs and pharmaceutical products, including medical practitioners, pharmacists, importers, manufacturers and distributors. Legislative and regulation play an important role in ensuring that pharmaceutical products are acceptable safety, efficacy and quality.

In CEECs, drug legislative and drug regulatory system has been established partly before the socialistic political system and partly during this period. This system has correspond with the socio-economic environment and had not been harmonised either within COMECON or with EU. The transitional process has brought new socio-economic environment and drug legislative and regulatory does not correspond with new situation. It is the reason that the drug legislative and the role and scope of the drug regulatory authorities are being step by step changed, especially in the field drug registration, pricing and reimbursement.

### **Legislation**

Generally, it is possible to say that according the current legislation in CEECs, introduction of a new drug on the market is possible only on condition that it is registered. But the drug legislation in many countries does not correspond with the current situation and needs. In some countries, the new legislation has been introduced, but only the Czech Medicinal Act seems to be harmonised with the EU regulations. Mainly is the legislation framework outdated and it causes the lack of transparency and instability in the registration requirements.

In the current situation, there are two directions in drug legislation process:

1. The first is to introduce Medicinal Act with many details and requirements for registration including the fees. This situation could lead to the procedure and requirements according the old socio-economic system.
2. The second trend is the opposite - issuing the short legislation framework for drug regulation, but sometime it does not include the clear rules for all subjects involved in the drug regulation process, e.g., duties and rights, appeal process, etc.

In both trends is the political and economical problem for acceptance the EC Directives and Guidelines, because the approach of the decision-makers. The acceptable solution could be in the compromise:

Introduce the optimal legislative framework for drug regulation (including drug registration) compatible with EC Directives, clearly define the basic rules for all participated subjects, establish the independent Medicine Agency with appropriate responsibilities and transparent registration procedure without economical and political influence.

The second step is preparing and introducing the sub-law regulations with more details for registration process and requirements. This regulation could established very detail requirements, steps of registration procedure, requested documentation, samples, etc. This system is more flexible and could be easy changed in the correspondence with the new situation.

Last but not least, the very important part of drug legislation shall be the clause which empowers the drug registration authority for accepting the EU registration procedures.

### **Applicant/holder of marketing authorisation**

In most medicine legislations in the CEECs, the applicant for registration and holder of a marketing authorisation has been defined as a manufacturer. The last development in the pharmaceutical industry (globalisation, internationalisation, mergers, etc.) leads to the problem with the identification who is really the applicant and holder of a marketing authorisation. In many cases, the product is manufactured in different facilities of one producer, in other cases after the merger of the companies the production is transferred to the join company and the identification the producer and holder of a marketing authorisation is very difficult. It causes the additional problems connected with pricing and reimbursement. The EC Notice to Applicants defines the applicant:

A (legal) person or company making an application for marketing for authorisation. If successful, an applicant becomes a marketing authorisation holder.

The holder of a marketing authorisation could be defined as the person (legal entity?) responsible for placing the medicinal products on the market.

But it causes some important questions. Could the holder only be the person? Or should it be the manufacturer, his representative or the joint company? Can we recognise the representative of the company in our country? Could be the holder limited company in our country? If the same product (identical) is produced by one company in different countries who will be the future holder of a marketing authorisation?

The proposed definition could be:

“The holder of a marketing authorisation is the legal person responsible for placing a medicinal product on the market and ensuring that the product will be marketed under approved specifications.”

To clarify this definition is very important in connection with the labelling, as the holder of the marketing authorisation should appear on the labelling.

### **Need clause**

Very often is the process of registration connected with the pharmaco-economic evaluation and the price of medicinal product could be the reason for refusal of the registration. In some countries is the tendency for limitation of the drug register and requesting the price evaluation in the registration process.

This situation could lead to the deficiency of the new medicinal product on the market and the potential patient could not have the access to the modern pharmacotherapy.

The optimal solution could be strict separation the scientific evaluation process of the drug registration and the pharmaco-economical evaluation. If the medicinal product meets all requirements for safety, efficacy and quality shall be registered. Pricing and pharmaco-economical evaluation should follow the registration according the reimbursement system

### **Target approval time**

Generally it is possible to say that in associated countries is not established the Target Approval Time in legislation. In some cases when it is, the Target limit is not possible to be kept, because the overloading and backlog in the Agencies. After the political changes, the pharmaceutical market has been opened and a lot of pharmaceutical companies started to launch their product on the market. It has caused the enormous increase in the number of applications. The Agencies have not been prepared for it. Legislation was not very clear, registration fees are generally very low and the result is delay of the registration process. Because of the very low fees, many companies have submitted a lot of products for registration without intending to launch the products on the market. The result is the gap between registered drugs and really marketed drugs.

The solution should be in the introduction into the registration process which regulates Target Approval Time (real) transparent procedure with “Clock Stop”, and

the applicants should set up their priorities - not to register all mainly obsolete drugs.

### **Chemical, pharmaceutical and biological documentation**

This part of the documentation (Quality) is very important. The contents are usually very similar with the standard format for applications in EC. The problem is with the part II B - Method of Preparation. Applicant sometimes refuses to submit the data concerning the methods because of the confidentiality. But the drug regulatory authorities need the technological data in order to evaluate the possible influence of the by-product impurities or intermediate on the quality and safety of the product. The compromise could be introducing the measures by the agencies to protect the confidential data of the applicant. The other solution could be to request not all details about the methods of preparations. The documentation shall contain all information about technology, which could have an influence on the safety and quality of the final product.

Parts II C, II D and II E - Control Tests are very often outdated without the validation. Those documentation accompanies the older products and generics. The applicant submits the documentation from the first marketing authorisation, which has not be innovated. But the registration requirements have changed according the new scientific knowledge in the safety, quality and efficacy of the medicinal products. In the other hand, the application for registration in CEECs is very often the first application. It is not possible to establish double standard for the safety, efficacy and quality. One for older products, other for new product especially in the case when the application is submitted simultaneously.

Bioavailability and bioequivalence documentation often causes problems in the evaluation process. The applicants cannot submit the bioequivalence data for the generic product based on the well-known active substance, or bioequivalence is insufficient (small number of trials, etc). They request to accept the documentation without bioequivalence data because of the existing list of active substances, not needing bioequivalence studies. But the list is not internationally approved and additionally the conditions for bioequivalence studies have already changed.

The recommendation is to harmonise the list of the active substances, whose do not request the bioequivalence studies and respect the current requirements for bioequivalence. Accepting the Mutual Recognition System by CEECs may solve this problem.

### **Summary of product characteristics**

The purpose and the scope of the SmPC is set out in Directive 83/570/EEC: “it is necessary, from the point of view of public health and free movement of medicinal products, for the competent authorities to have at their disposal all useful information on authorised medicinal products, based in particular on summaries of the characteristics of products”.

It is the definitive statement between the competent authority and the marketing authorisation holder. This SmPC is a basis of information for prescribers and usually is the resource for Patient Information Leaflet. In CEECs,

this part of documentation has not been well appreciated. The structure and content have been different with many variations.

The question is if it is possible to accept the SmPC approved in country of origin or to request the specific SmPC for a country where the application is submitted. It seems to be that after accepting the EU format of SmPC could be recognised the format approved in country of origin. But in local language shall be requested because of the further information for the prescribers and the patients.

### Expert report

Very often the question in Central & East European countries is for which type of applications an Expert Report is required. Many applicants complain that for the abridged application the Expert Report is not necessary.

The Notice to Applicants requests the Expert Report for each of Parts II, III, and IV for all types of applications. As appropriate, Expert Reports may be abbreviated for an abridged application.

This should be the basis for harmonised registration requirements in CEEC:

- the Expert Reports shall be requested for all types of applications
- the abbreviated form may be requested for abridged application
- the Expert Reports of the original marketing authorisation holder may be used
- the format shall be according the Directive 75/319/EEC.

### Certificates

The application of GMP rules in the manufacture of medicinal products is one of the most important prerequisites for product approval. Generally, there is no written request for the GMP certificate as part of the submitted documentation. Only a Free Sale Certificate is requested in some countries.

This difference may cause some problems in the evaluation of the products. There is a lack of confidentiality for the manufacturing process and quality and safety assurance by the manufacturer. Some manufacturers submit the certificate according to ISO 9000 - 3. This certificate is not sufficient as it confirms only the quality system, not the standard quality of a medicinal product. This requirement could only be assured by strict application of GMP rules.

On this basis, the GMP certificate is strictly needed for the drug evaluation. The WHO form is recommended and mainly accepted. It could reduce the unnecessary retesting of samples or inspection of the manufacturing site.

Also, the certificates for active substance(s) and excipients are needed. Contrary to the WHO recommendation, the producer or supplier of starting materials shall be identified and the standard quality must be assured. Every change in the quality or supplier of the starting materials shall be notified to the competent authorities.

### Registration samples

Usually, and in accordance with Directive 65/65/EEC, Article 4, samples of the active and non-active substances and of the finished medicinal product must be supplied with the dossier. In some cases, samples should be provided at the request of the competent authorities.

The problems are:

- the quality of the final medicinal products
- the type and quantity of the active substance, and reference standard, impurities and degradation products.

The recommendations for samples could be:

- The final medicinal products shall be in the sufficient quantity to permit a full assay and verification of the control methods used by the manufacturer. For expensive medicinal products, the applicant may send a reduced number with a reasoned justification.
- The quantity for each active substance: 5g
- The quantity for reference standard: 0.5g
- The quality for each impurity: 0.05g
- The quantity for each degradation products: 0.05g

This could harmonise the requirement for sample verification of the control methods and avoid non-necessary retesting.

### Local clinical trial

The dossier must contain the Part IV - Clinical documentation in accordance with the Notice to Applicants. If this part has been evaluated by competent authorities on the high scientific basis and approved, there is no reason for local clinical trial -to repeat the previous results. But in many CEEC still exists the requirement for local clinical trials because of the safety. It seems to be that the main reason for it is to be familiar with new medicinal product and to receive the free samples. This tendency is not in accordance with the harmonisation and free movements of goods.

Pre-approval clinical trials are also requested by the registration of the generics. Sometimes is difficult estimate if the application is generic application, or application of new active substance. In some cases the applicant submits the product as the generics, but in the country these is no registered the original product. From this point of view, the generic seems to be as an original product and should be evaluated as the original product.

Other problem is by the evaluation of the licensed product, or in the case when applicant has bought the documentation from other company. Could be accepted the clinical trial based on the other product, or the applicant shall submit his own clinical trial?

It could be recommended that:

- the local clinical trials should be very limited or fully avoided
- the documentation of clinical trials must be in accordance with the Notice Applicants and based on the GCP rules., the possible inspection by the competent authorities is recommended
- case report form may be submitted upon the request of the competent authorities during the evaluation

- the ICH guidelines shall be taken in consideration.

### Labelling and leaflets

Labelling and leaflets are the important part of the registration dossier. There are a lot of differences among the CEEC in the requirements for registration. On the one hand, the competent authorities request mostly the labelling in local language, but the content of information on the outer packaging are very different from the Directive 92/27/EEC. Sometimes there is no difference between immediate packaging and outer packaging or the hospital packaging. Very often there is not enough information on the immediate packaging or too much on the outer packaging.

Many problems are in the requirement for the name and address of the holder of the marketing authorisation, the number of the marketing authorisation or the excipients. Sometimes the national legislation requires the additional information e.g., the unused medicines shall be returned to the pharmacy. The manufacturers in many cases do not like to respect the requirements for local language, because of the economy and small market size.

Very similar situation is concerning the user package leaflets. In CEECs, there have not been the strict requirements for patient leaflet, the requirements for local language and there were a lot of differences in the content of the user leaflets. Recently these countries started to introduce the user leaflet, mainly in local language, but the content has not been harmonised with EU roles yet. It causes the problems with multilingual leaflets.

The recommendation is that:

- the labelling shall be in accordance with Directive 92/27/EEC and no additional information requested
- the labelling may be bilingual
- the patient leaflet shall be in accordance with Directive 92/27/EEC and be written in the local language
- if the content of user leaflet is harmonised, it may be multilingual.

### Renewals

The marketing authorisation is generally in CEEC valid for five years like in EU countries. In accordance with Directive 65/65/EEC no later than three month before the end of five years, the marketing authorisation holder shall submit the application for renewal.

The renewal should not be confused with the procedure for variations. It is an independent procedure and operates for different purposes.

In many cases, the holder of the marketing authorisation does not submit an application for renewal. He explains that all changes have been included in already submitted variations and there is not necessary to submit the application for renewal.

There is the obligation for holders of a marketing authorisation to submit the application for renewal because of legal validity of the marketing authorisation.

On the other hand, there is the problem with the quality of the dossier for renewal. The holder of a marketing authorisation in many cases only submits the formal application for renewal, without the updated documentation.

He gives as reason that the product was approved 10 or 15 years before, when the registration requirements were different. But the holder of the marketing authorisation is required to update the marketing authorisation throughout the life of the product, taking into account all new technical and scientific factors concerning quality, safety and efficacy. These updates shall be done through variations. If not, they must be done through the renewal.

Another question in the CEECs is whether the marketing authorisation is valid after the expiry date without approval being granted in cases where the applicant has submitted the application in time. This happens sometimes because of the backlog at the competent authority. This should be the problem of the competent authorities. The holder of the marketing authorisation has fulfilled his obligations. The application for renewal could be supported by the following documentation:

- an updated part I A
- periodic safety updates and pharmacovigilance data
- list of all variations
- update of the quality according to the current scientific and technical level and guidelines
- the current SmPC.

It is recommended to submit the application for renewal minimum three months before expiry, but in some CEECs it is requested six months before that date because of the backlog.

The documentation should be updated especially in the part of safety and quality, including all variations.

### Conclusion

The Drug Regulatory System has significantly changed in the Central & East European countries over the past years. The development has been different in these countries and it has caused a lot of differences in the registration is not always transparent and finished on time requirements. This situation is an obstacle for the registration process which is contrary to the free movement of goods, not only between EU countries and CEECs but also among these countries. That is the reason why harmonisation is needed. The basis for it should be EU legislation, to be incorporated in the country's drug legislation.

In the presentation, some solutions have been proposed in order to harmonise registration requirements while respecting minor differences in some CEEC. But these differences must not have an influence on the whole registration process and on the standard of the safety, efficacy and quality of drugs. The main goal of this process is to avoid double standards as requirements for safety, efficacy and quality must be similar everywhere.

### DEBOYSER:

Dr Martinec, I think you have very well described what might be called the "European model" for the authorisation of OTC products. A striking feature is of course that they are submitted to exactly the same process as any other medicinal products, i.e. a full dossier needs to be submitted and they are regulated under the same rules.

However, that does not mean that there is not some flexibility with regard to some classes of medicines, and I would like to invite Prof. Paál to describe the case of herbal medicinal products.

## PAÁL:

### Actuality of the issue

Hungary has great traditions in phytomedicine. The 7<sup>th</sup> Hungarian Pharmacopoeia, still in force, contained 70 monographs of herbal medicinal drugs, 15 monographs of essential oils as well as 27 herbal medicinal products (alcoholic and dry extracts as well as *species*, i.e., tea mixtures). In the past, registered „herbal medicinal products” comprised „medicines” (e.g., extracts from *Ginkgo biloba*, *Serenoa repens* and *Silibum marianum*) and “paramedicines”. The latter legal category comprised products of natural, mostly herbal origin that might be sold both in pharmacies and herbal shops. The 25th Act of 1998 on medicines for human use introduced the European Union definition to medicines; thus, the paramedicine legal category was abolished. It means that no such products submitted after 1 January 1999 may be registered while those registered or submitted before this date must be reclassified as medicines or other legal categories (food supplements, foodstuffs or cosmetics) before 31 December 2004.

Thus, a marketing authorisation (MA) for a herbal medicinal product means:

- assessment and MA of new herbal medicines
- re-qualification and MA of former herbal paramedicines.

In June, 1999 there were:

- 277 registered and marketed paramedicines (including, among others, Hungarian innovations, German and Austrian non-prescription medicines, Ayurvedic medicines, etc.)
- 40 registered paramedicines without a valid MA (e.g., final sample has not been submitted yet),
- 187 items submitted late 1998, waiting for evaluation and MA.

### Definition of herbal medicinal products

The Medicines Act has required a new Minister of Health Decree on MA of medicinal products (drafted) [1]. It is expected to be issued in 1999. It contains the following definitions.

Types of medicinal products (level of processing):

- substances of:
  - human
  - animal
  - herbal
  - micro-organism
  - chemical origin
- preparations (dosage-forms).

Types of medicines (principle of the therapy)

- homeopathic
- allopathic.

Homeopathic medicinal products are not reviewed in the present work. Herbal medicinal products are part of natural ones, as indicated below:

- *Natural medicinal product*: any medicine containing an active principle of mineral, animal or herbal origin (or a mixture thereof), independently from its (their) processing level (rough or partly processed) [2].
- *Herbal drug*: over- or subterranean part of a medicinal plant or its product processed according to the Hungarian Pharmacopoeia [3].
- *Medicinal product of herbal origin*: any medicinal product containing, as active substance, (one of the) following substance(s) exclusively: powdered herbal drug, rough or purified extract or a substance manufactured thereof [2]. I.e., medicines containing also synthetic substances are not qualified as medicinal products of herbal origin.
- *Herbal medicinal product*: any medicinal product containing as active principle(s), herbal drug (or a mixture thereof), independently from the fact that it is (they are) not or partly processed (rough, dried, partly processed such as essential or fatty oil, resin, etc.) [2].

This paper outlines the marketing authorisations of herbal medicinal products.

### Marketing authorisation and renewal of new herbal medicines

Rules governing MA and renewal of any medicinal products applied with the following differences.

- Chemical and pharmaceutical dossiers (characterisation, manufacture and testing): the EU Guideline EEC 3AG22a is incorporated in the MoH Decree [1].
- Safety and efficacy dossiers: bibliographic submissions (according to Directives 65/65/EEC and 75/318/EEC) may be accepted but their content assessed. As for details, see the MoH Decree on re-qualification of paramedicines (drafted) [4].

Renewals: like other medicinal products. Expert Reports are requested according to the above mentioned rules.

### Re-qualification of paramedicines into non-prescription medicines

A new Ministry of Health Decree on the requirements for re-qualification of paramedicines into non-prescription medicinal products has been drafted [4]. It is expected to be issued in late 1999.

Products with a *medicinal (therapeutic) claim*, differing from a „health claim” may be re-classified as medicinal products. The latter comprises claims maintenance of health and beauty (also by helping in prevention of deficiency diseases providing vitamins and/or minerals in limited quantities).

Requirements for the re-classification are outlined as follows. The present documentation must be supplemented or new documentation must be submitted as indicated below.

- Their *manufacture* is possible only by holders of manufacturing authorisation in facilities which are in strict, certified compliance with GMP. (Paramedicines might be manufactured also by others and less strict GMP was applied, e.g., no qualified person was required).
- Their *quality* (pharmaceutical-chemical) dossier must follow the rules described above for marketing authorisation of new herbal medicines (EEC 3AG22a).
- Their *safety* may be established on the basis of literature data on the herbal components (experimental toxicology or human clinical data [2, 5-6]). In case of more active substances, the Expert Report (see below) should contain arguments why toxic interactions between the herbal ingredients are not expected. “Established use” as a proof for safety may only be accepted if the effectiveness of the adverse reaction monitoring system of the county (countries) where the marketing has been taking place is demonstrated.
- Their efficacy may be proven by:
  - bibliographic references according to Directives 65/65/EEC, 75/318/EEC, on animal pharmacology and human clinical experiences (see below). Monographs of internationally recognised scientific bodies (such as ESCOP) and documented, reasoned decisions of regulatory authorities (if the National Institute of Pharmacy was convinced that their scientific standard is of the same level as in Hungary) may be taken as bibliographic references. Moreover, data collected from the literature and summarised in an Expert Report may do if it is proven that they may be extrapolated to the product in question. In case of combinations, however, the more the active components are the less is the probability that literature data on the individual active principles could be extrapolated to the combination product. At any rate, the scientific rationale for the composition and detailed explanation why data on individual components may be relevant to the product is a prerequisite for the MA;
  - human clinical experiences that may be clinical trials (double-blind > single-blind > open, controlled > uncontrolled, probability of acceptance of those on the left side of the > symbol is better than those of the right side) strictly documented individual treatments, etc. [2].
- The Summary of Product Characteristics (SmPC), the Patient Information Leaflet (PIL) and the labelling must comply with the requirements for medicines (identical to the EU ones). (For paramedicines, SmPC was not required, short PIL-like text was often written on the outer packaging exclusively).
- Expert Reports (meeting the EU requirements for format and content) as well as the draft of the Assessment Report should be submitted.

## References

1. Decree No. ... of 1999 of the Minister of Health on marketing authorisation of medicines (drafted).

2. WHO Research Methodology for Evaluation of Traditional Medicine. Working material. WHO, Geneva 1997.
3. Hungarian Pharmacopoeia, 7th Edition. Medicina, Budapest 1986.
4. Decree No. ... of 1999 of the Minister of Health on re-qualification of paramedicines to medicines (drafted).
5. Guidelines for the assessment of herbal medicine programme on traditional medicine. WHO/TRM/91.4, Geneva 1991.
6. Research guidelines for evaluating the safety and efficacy of herbal medicines. WHO WPRO, Manila 1993.

## DEBOYSER:

We have now seen the European model of full authorisation of OTC products, sometimes slightly facilitated in the case of plant-based products as explained by Prof. Paál. The alternative is perhaps the monograph system of which I think the United States is a good model. This will now be presented by Dr Murray Lumpkin.

## LUMPKIN:

Dr Lumpkin described both systems for marketing OTC medicines in the USA (a) the monograph system and (b) the product-specific full authorisation system, including Rx-to-OTC switches [see also Dr Lumpkin's presentation on this subject (page 88)].

## DEBOYSER:

I now open the debate to the floor

## HILDEBRANDT:

With respect to monographs, we have in Germany a similar situation, as Germany has for a long time looked more across the Atlantic than towards Brussels or London. We started in particular by re-establishing the dignity of the substances available on the market before the Medicines Law came into effect, and we also tried to work with monographs. The problems with monographs, however, was that we only got restricted information from the companies. They presented information but not all of it. In contrast, in order to make better information available to the consumers, we started to develop the system of “Muster”. This is information based on dossiers obtained during the full licensing process. We are recommending companies to provide these “Muster” which are continually updated by the Institute. In addition, there is the so-called “*Standard-Zulassung*” – I believe something specific to Germany – which relate to a lot of compounds regulated by a recommendation from the Institute but probated by a Commission and finally by Government or Parliament. This allows us to cover all information on medicines used in pharmacies and hospitals not directly commissioned by a licensing or registration process. The normal situation in Germany is of course that we are licensing products as is usual within the EU through single-licence processes.

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**EBERWEIN:**

I agree with most of what Prof. Hildebrandt just said except that industry did not submit all data when the monographs were evaluated. We, i.e. the association BAH, invited and encouraged industry on several occasions and I believe that many companies did actually submit data. I agree that the "Muster" are very important and think they could be a model for Europe, i.e., they could be taken as a basis for bibliographic applications. In fact, AESGP in the early 1990s made proposals for a similar system of monographs under the title "*Passport for Europe*". I would like to highlight again that these proposals could have served as European models for widely used OTC ingredients.

I also welcome what Professor Paál said on the registration of herbal medicinal products. He also highlighted the monographs and his example was very enlightening. I believe you will also accept the WHO monographs, which could also be a model for a European procedure.

One other point concerning what Professor Martinec said earlier. I believe that the registration procedures in Central & East European countries are overall in a good shape and are carried out by highly motivated people. However, what I missed is the timing. I understand that there are no time limits fixed in the national Medicines Laws, and believe that it would be advantageous to have a clear time frame for the authorities' decision-making. In the EU there are such time limits. They may or may not be met by the authorities, but the principle of time limits could be proposed for Medicines Laws in other countries.

**PAÁL:**

Hungarian has a monograph system which is practically the same as in the United States. I almost agree with you, Dr Eberwein. There are different monographs. The WHO, ESCOP or German E-Commission monographs are not the same but we accept all of these as literature data. However, in some monographs there is a (positive or negative) decision, and in others there is no decision but only data. In the latter case, we can of course only accept the data.

**MARTINEC:**

Concerning time lines, only three countries have included these in their Medicines Law:

- Czech Republic – 18 months
- Hungary – 24 months
- Slovak Republic – 210 days.

For example, in the Slovak Republic there are for the moment more than 1 000 applications. It is therefore extremely difficult to meet these time lines. For new applications however we are obliged to respect the timing. There are some complaints concerning old applications whose registration is sometimes postponed.

**RÄGO:**

In Estonia, a time limit of nine months has been in the law since 1996, and how the time limits are followed in our country can be found from the Agency's website. You will see that in 89% of cases the 9-month time limit is perfectly adhered to.

**DEBOYSER:**

In the EU, the time limit is 210 days (which is closer to seven months than to nine months), and the applicant countries will have to meet this target by the time they become members of the European Union.

**SCHOLTZ:**

Concerning the establishment of monographs in the United States, I have the following question. While it is obviously fairly straightforward once they concern relatively well-known substances, very often we observe that products are being combined. There might be a manufacturer wanting to bring two well-characterised products to the OTC market in a combination that does not yet exist. So my question is what would be the procedure and the timeline, and the decision-making process, i.e. whether you first classify it as prescription-only or whether you would go straight for OTC.

**LUMPKIN:**

There are several different avenues. There are certain combinations that are permitted under the monograph system. This means that the monograph simply allows certain combinations to happen, and people can pick and choose and put things together. If there are new combinations and new safety issues, these would have to come through the new drug application (NDA) timelines and decision-making process. There are certain benefits for a company wanting to come through the NDA process as we as FDA are working one-on-one with the company and there is a certain degree of data protection for the company prior to the time a decision is made. Companies, in addition, obtain market exclusivity after approval if they qualify for this. All this is not true under the monograph system, which throughout is very open and very transparent and where all the data are in the public domain. People who like your product can add more data to the process, whereas people who do not like your product can also add negative material to the discussion.

**DEBOYSER:**

The beauty of monographs is of course that they lend themselves very well to a universal trend and that they can be useful for countries not wanting to carry out a full evaluation of well-known substances. Perhaps it would be worthwhile discussing the current status of the WHO monographs on herbal medicinal products.

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**FROM THE FLOOR – REINSTEIN:**

I do not think that the distinction has been made very clearly between the monograph system in the United States, where you simply put a product on the market based on not only the monograph but also on Good Manufacturing Practices (GMP), and Europe where, even if there is a monograph, you still have to submit the product for registration and get the analytical and stability part pre-approved before marketing. I wonder if the regulators could comment on what they think is the possibility of having no pre-approval based on GMP in Europe.

**DEBOYSER:**

We would certainly have to change the system fundamentally, which I am not sure we are prepared to do for the moment. However, this is something we could discuss in the context of the evaluation of the current marketing authorisation system which is due in 2001. It is mainly in the context of the proof of efficacy that we are prepared to look at monographs – at least for well-known substances.

**HILDEBRANDT:**

In principle, when looking at monographs, above all efficacy and safety are covered. The law requires pharmaceutical quality to be established case by case to be acceptable. When looking at the variety of auxiliary compounds going into each medicine, this information needs to be available. In addition, it also allows companies a certain degree of difference in technology and compounds.

**FROM THE FLOOR – SOLLER:**

An important aspect of the monograph system in the United States is that in many monographs, final formulation testing is specified. For example, in the internal analgesic monograph there is a specification that the analgesics must meet the disintegration and dissolution requirements of the US Pharmacopoeia. In other monographs this is not specified. However, FDA will not issue a monograph unless there is a USP monograph.

For instance, in the monograph for fluoride in dentifrices for the prevention of caries there is a very sophisticated final formulation requirement and linkage to the USP, with reference standards provided by certain companies. Those reference standards were initiated about 15 years ago and the companies have promised in order to make this system work that they will always provide this same standard. This means that two or three biological tests are required for that specific formulation. Although there is not that same level of final formulation testing for every type of product, there are technical standards that are closely tied in to the GMP as monograph requirements. If you as FDA then inspect the product, and the company is found not to be following that final formulation testing, the product can be deemed adulterated and/or misbranded.

**ŠMÍD:**

We have a similar monograph system for switching in the Czech Republic but it is still in the very beginning and not for all categories of medicinal products. We consider such a system as very advantageous from the point of view that there is an existing standard. However, if there is an interest to go beyond that standard, this is possible if some additional data are provided, giving additional feedback for the development of a monograph system. If such a monograph system were to become truly international, we must remember one issue which is very critical, i.e. data exclusivity. The monograph system can in principle only be developed if there is harmonisation in data exclusivity protection between different countries. Otherwise a situation may arise where, because of specific data protection, the monograph cannot be used in some countries.

**SCHOLTZ:**

Professor Martinec, is the need clause still part of your system, i.e. do manufacturers still have to prove that the product they bring to the market has an advantage over other products? If that is the case, you are of course limiting the number of products on the market and consequently the competitive pressure with ultimate effects for the economy.

**MARTINEC:**

I think that this is not a general requirement in Central & East European countries. In Slovak law there is such a provision, but it is not a requirement for applicants to submit such an evaluation. It allowed the authorities to refuse certain products but this provision will soon be abolished in an upcoming amendment of the Medicines Law.

**DEBOYSER:**

Such a need clause would indeed be incompatible with existing EU legislation. In fact the only country having such a provision until recently was Norway, and Norway had to give this up when it became a member of the European Economic Area (EEA).

**FROM THE FLOOR – HERXHEIMER:**

I would like to ask the regulators what is the evidence for the efficacy of individual products. This is very difficult in the case of OTC products but the regulators should have such evidence for each product. What arrangements do you foresee in the future for making that evidence accessible to the consumers? The fiction maintained for many years is that the professionals are entitled to have proof of efficacy, but manufacturers are often reluctant to disclose the complete evidence. It is now becoming more and more accepted that professionals need the evidence for different purposes from the purposes for which regulators need it as they need to think about the medicines intelligently. I think that with your whole push for recognising that consumers have responsibilities and want to be responsible for their own health, this argument applies in exactly the same way to consumers. Therefore, the con-

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sumers need to have access to the full evidence for efficacy of the products they are offered over the counter. There is however no sign of this evidence being available in the world. How do you see progress with this problem?

**MAZUREK:**

In Poland, like in many other countries, there is a distinction between medicines and food. However, in our law no category of borderline products exists. This situation creates many problems from the point of view of evaluation approaches, especially regarding clinical evidence for therapeutic efficacy.

The Drug Registration Committee has implemented many internal procedures that help to solve that problem without braking the framework of the Polish pharmaceutical law. A simplified procedure is therefore applied to products containing vitamins and minerals. Here a crucial factor is both the content of a particular active ingredient as well as the composition, i.e. monograph-component v multi-component products. The evaluation in this case is made based on the relation to the RDA value as well as to the kind of vitamin (water-soluble v water-insoluble) and mineral.

Moreover, the Drug Registration Committee has introduced a simplified registration procedure for a special category, the so-called therapy complementary products. Those products are likely to be active, based on the composition and possible mechanism of action, but they do not have complete clinical data. Here many products can be found containing natural ingredients in a variety of mixtures. In each case, the toxicological, chemical and pharmaceutical parts are crucial for obtaining an eventual marketing authorisation.

All the products are pre-evaluated by a joint panel including a representative of the Drug Registration Committee, the Drug Institute, the National Institute of Hygiene and the National Institute of Food and Nutrition. Based on a product's composition, dose and claim, the panel preliminarily categorises the product into the food, cosmetics or medicines category.

Cosmeceuticals are treated as medicines and registered as regular medicines using a simplified procedure.

The increasing interest in borderline products highlights the future need for relevant changes in the Polish pharmaceutical law. Many OTC products such as simple, unprocessed parts of herbs or homeopathics are exempted from registration in Poland. Here, a marketing authorisation from the Drug Institute is an obligatory requirement to put the product on the market.

**DEBOYSER:**

This is of course only a partial answer to Andrew Herxheimer. In Europe, we now have in the centralised procedure the European Public Assessment Report (EPAR). I do not know whether this meets all your wishes but it already provides the beginning of an answer. I would also like to ask Professor Hildebrandt, as current Chair of the Heads of Agency, about plans to adopt a Public Assessment Report in the context of mutual recog-

nitition. I believe there have been discussions on this already.

**HILDEBRANDT:**

We are trying to establish core-SmPCs for certain substances, which is somewhat related to the monograph situation. It is however not easy to establish these core-SmPCs as not only the regulators sometimes have problems to harmonise but it is also in the hand of the companies to harmonise. The EPAR in the centralised procedure is a very important information tool for the consumer, which can be established thanks to the legal privilege but also to the material support from the European Community and the Member States for both List A and List B compounds. As for the mutual recognition procedure, this will eventually be done. However, it will of course also depend on the Member States. As each Member State will already have a national licence, this of course demands that each Member State should be in the legal, material and intellectual position to do so.

When looking at the number of compounds, we see that in the centralised procedure, so far around 200 licences have been issued since 1.1.1995. In Germany there are around 3 000 decisions each year. So just imagine having to issue 2-3 000 European Public Assessment Report (EPAR) per year. This by far outweighs the current structure in Germany, and other countries are in the same situation.

The issue raised by Andrew Herxheimer is important and of concern to all of us. It appears that we sometimes have a different view concerning efficacy. A possible definition of efficacy may be "the probability of the appearance of a desired effect different from chance under the situation of application". This is a numeric approach, however, this approach which allows to count the significance of the verum against placebo demands that you are able to have a collective which is countable and belongs to an ontological picture of a certain disease. This is however not always the case. In Germany and in other countries in central Europe we did not always appreciate the Anglo-Saxon or numeric approach. At that time certain scientists in Vienna, France, etc. did not look for an ontological disease as such but rather at a process. They did not talk about disease but rather about disturbed physiological processes. This means that they were looking for symptoms and a rational physiological approach on the individualised patient, and did not want to accept a numeric average value for a certain number of patients. However, there are individuals left or right of that average number which would not fit in the usual clinical experiments. This kind of thinking still persists among physicians, not only in Germany and France but everywhere as you have to deal with patients and do not always believe in average numbers obtained from clinical data.

With this we are faced when looking at old compounds. We get many physiological data related to processes but not to experiments carried out under certain well-established criteria. Today in Europe we have adopted this numerical approach but we know that we do not have these data for all compounds existing in the market for a long time. This explains why industry could not

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supply us with all these data as I mentioned earlier. Nowadays we try to demand all these data in the CPMP efficacy working party. I am interested to provide specific guidelines so that industry and regulators know how to approach the efficacy issue. This is however a wide field and we have to obtain from industry as a minimum is plausibility, objectivity and completeness of the data.

**LUMPKIN:**

I think Mr Herxheimer has touched on a very important point about the ability and need to have consumers play a role in the decision making and giving them access to the data for the decision-making process so that they understand what is behind the regulatory decisions that we make. I think we have tried to approach this in several ways in the United States. In the monograph process itself, the data are completely transparent, and FDA's regulatory decisions have to be explained in the public record. People might of course disagree but this is perfectly OK in an open society. In the application process, after an application is approved there is an electronic freedom of information (FOI) law that requires that the report of that decision and the analysis of how it was arrived at be made available electronically. It can therefore simply be downloaded from the website. Our challenge is therefore a resource challenge to get FOI data available in a timely manner and an education challenge to help people understand where these data are available and how they can be accessed.

All FDA's public advisory committees are required to have consumer members nominated by the Consumers' Union in the United States. These committees also often have patient representatives so that when discussing diseases that are treated by prescription products there are patients present who bring another dimension to the discussion. These individuals help FDA understand what the influence of its regulatory decisions could be in the patient and consumer world.

**RAINE:**

This is very difficult issue and we have to recognise that over the 30 years European legislation has been in place, there has been a complete sea change in expectations on the part of consumers and health professionals for information. We have to accept this but should also recognise that we are in a different world.

When it comes to the legislative basis, we have talked a lot about efficacy and there has been a theme of rather arbitrary efficacy levels. From the regulatory angle, the education process has to address a much more difficult understanding, i.e. the risk / benefit evaluation for the individual. This is a difficult enough process for the regulators, so for the consumers it is even more difficult, and this is something we should not lose sight of.

The EPAR is of course a model. However, the renewal of the marketing authorisation, particularly if the focus is on old products, is when we look to re-evaluate the therapeutic place of that medicine. In the EU we do this every five years and in the United States I gather it does not happen at all. We are thus every five years in a position to look at risk and benefit, but with 3 000 appli-

cations a year as is the case in Germany we cannot do a "Rolls Royce", i.e. a wonderful job. The UK perspective is therefore that we have to prioritise and look to areas where evidence needs to be produced. One such area in the UK for the moment is medicines in children. Once we know where we need to provide better evidence, and we actually have a process and a procedure to do that, maybe a "renewal EPAR" will become possible and move us towards the ideal world.

Renewals are being looked at in the "Notice to Applicants" working group so that we do have a more uniform approach to the European renewal should there be an expert report to aid the process of evaluation.

To sum up, work has to be prioritised, the regulatory system has to catch up, there need to be more resources but we have to be realistic. Risk / benefit is what the consumer needs to understand and not just arbitrary efficacy.

**DEBOYSER:**

In my opinion, it boils down to what is the evidence for efficacy which is claimed in advertising, so that people know that when they purchase a product the claims are actually scientifically sound.

**FROM THE FLOOR – HERXHEIMER:**

What Professor Hildebrandt said does not greatly help the situation. If the efficacy is defined in old-fashioned terms of what physicians believe and observe and the licence is based on these observations, that should be stated. When it is out in the open, then everybody can discuss it, improve it and agree on what is needed next to investigate that particular problem. I would say exactly the same to Dr Raine. It does not require great resources just to specify exists now. It is not so important to have benefit / risk evaluations afresh for everything. Let's just have a list of references on which the licensing decisions are based. The FDA freedom of information packages are of enormous help and support. Let's have that throughout Europe and the rest of the world. I do not see what is stopping you and do not believe this is an issue of resources at all because you have got the materials in your files.

**DEBOYSER:**

I think that it is really a question of what goes into the monograph. If the monograph really specifies the evidence to be used for claims, then it should be taken into account, and maybe we should have a more serious look at this section of the monographs.

**HILDEBRANDT:**

Concerning advertising, I agree absolutely with Patrick Deboyser. I was just demonstrating what kind of sources we have: the numerical part and the physiological part. What we are trying to do is of course to open it to the public. That's why these monographs are available. However, these old monographs were in Germany at least in part built on non-written but outspoken experience of the members of these committees. As this experience can

of course not easily be communicated to others, the government stopped the official use of these monographs and the "Muster" are related to data obtained from industry and from other sides. We try within our limits in terms of bibliographic evidence and in terms of efficacy to decide on a given situation. This does not allow you to give more data than you actually have. In spite of this, we try to be as transparent as possible.

## SECOND PART REGULATORS' FORUM

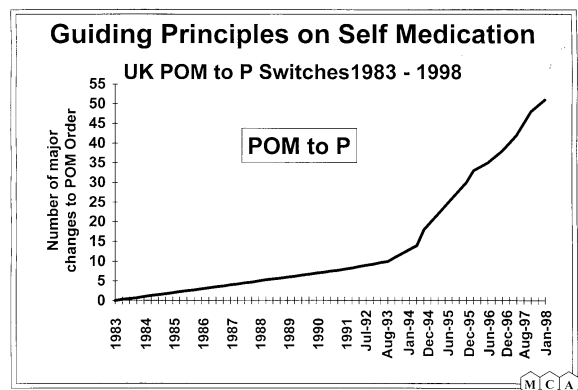
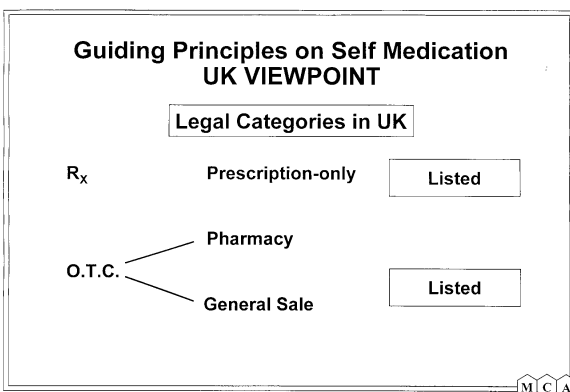
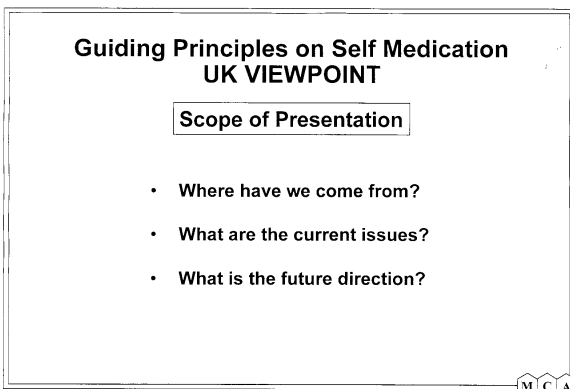
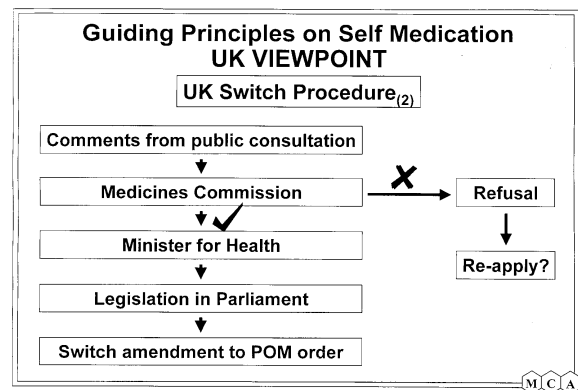
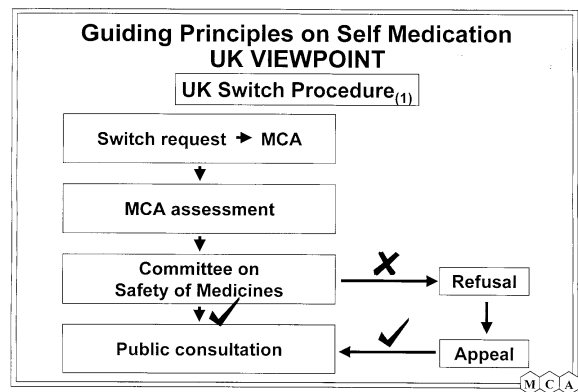
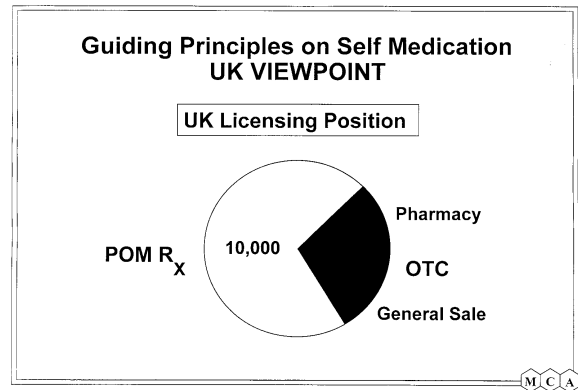
[Dr Lumpkin had to leave the forum at this point]

### SCHOLTZ:

We will now continue our discussion by addressing the issue of Rx-to-OTC switching, the use of brand names and the advertising of OTC products. Dr Raine, you have responsibility to oversee the 'switch procedure' in the United Kingdom. Please give us a brief overview of your experience.

### RAINE:

Switching, i.e. the change from prescription-only to OTC, is a very critical area for enabling more medicines to become available for safe self-medication. In fact we could say that it is the lifeblood of the OTC sector. I would like to give you a brief overview from the UK perspective of our experience, the problems, the lessons we have learned and where we see is our future direction now that we have the EC guideline.



## Guiding Principles on Self Medication UK VIEWPOINT

### Progress in Switching

- New indications - self-recognised
- New indications - initial medical diagnosis
- Prevention
- Removal of earlier switch restriction

M C A

## THE SWITCH CHALLENGE UK VIEWPOINT

### R<sub>x</sub> Criteria

- Direct or indirect danger even when used correctly, if used without medical supervision
- Frequent incorrect use
- Further investigation of activity and/or side-effects is required
- Parenteral

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### New Indications - Self Recognised

Examples:	Ingredients:
Enterobiasis	Mebendazole
Male pattern baldness	Topical minoxidil
Hyperhidrosis	Aluminium chloride hexahydrate

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### Lessons from applying switch guideline

1. "direct or indirect danger .... without medical supervision"
  - known ADR eg GI bleeding / NSAID
  - medical diagnosis required eg menorrhagia
  - community danger, e.g. antibiotics

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### New Indications - Initial Medical Diagnosis

Examples:	Ingredients:
Vaginal candidiasis	Topical / oral imidazole
Irritable bowel syndrome	Mebeverine
Pain of non-serious arthritis	Topical NSAIDs oral ibuprofen

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### Lessons from applying switch guideline

2. "Frequent incorrect use"
  - "upward" re-classification
  - formulation eg liquid filled gel capsule
  - active ingredient eg amyl nitrate

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### New Indications - Prevention

Examples:	Ingredients:
Prevention of cold sores	Aciclovir
Prevention of hay fever	Beclomethasone Sodium cromoglycate
Prevention of indigestion	H <sub>2</sub> antagonists
Prevention of spina bifida	Folic acid

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### Lessons from applying switch guideline

3. "further investigation of activity and/or side effects required"
  - premature switch applications
  - new chemistry, salt, pro drug, metabolite
  - unclear mode of action

M C A

## Guiding Principles on Self Medication UK VIEWPOINT

### Current issues - Regulatory

- Pharmacovigilance initiatives
  - pharmacist ADR reporting
- Clinical Trials in pharmacy environment?
  - considering legal issues
- EC procedures for switching?
  - Notice to Applicants Group

MCA

## Guiding Principles on Self Medication UK VIEWPOINT

### Current issues - Communication

- Quality in patient information
  - EC Readability Guideline
- Advertising
  - new MCA Guidelines

MCA

## Guiding Principles on Self Medication UK VIEWPOINT

### Future UK direction

#### "Public health focus"

- aspirin 75mg for CVS prophylaxis
- nicotine replacement therapy
- emergency contraception?

MCA

## Guiding Principles on Self Medication UK REGULATORY VIEWPOINT

### Conclusions

1. Access to safe self medication a key public health issue.
2. Switching from R<sub>x</sub> to P and P to GSL will continue to evolve.
3. Consumer expectations for quality information increasing and must be met.

MCA

## SCHOLTZ:

Thank you June for a very good presentation and on the good work you are doing. I believe that MCA's activities in this field and perhaps in post-marketing in general are a model not just for the rest of Europe but also for the rest of the world. We will now have a discussion on some issues directly related with switching, such as the advertising of switched products, the issue of the brand name of switched products and promotion in general. However, before we engage in this discussion, are these questions or remarks on the switching procedure?

## FROM THE FLOOR – SOLLER:

Dr Raine, if there is one issue that is holding up switch and creates a barrier in the United States is how the dialogue is engaged when there is a negative switch decision. I was very interested by the three questions you put up. My question is, how much do you elaborate on each category. For instance, in the United States we are faced at least for the cholesterol-lowering drugs with a negative switch guidance that gives no direction to industry as to why the data developed – which were quite extensive – did not answer the original benefit / risk question. When you are now forced to place a negative switch decision into a category, how much further elaboration do you give to the sponsor?

## RAINE:

We give a legal reason which is the criterion under the EC Directive which has been fulfilled, and then we give an elaboration on the scientific data, omission, lack or problem that we see. That is usually done in a dialogue with the company but they have a formal opportunity to appeal. The UK has always had the appeal procedure and although appeals on legal status applications are not set in our law, the natural justice principle means that companies should be able to come back and present further data to answer the problems. If you ask me what the success rate of the appeals is, it is not strong but I have known at least one product have two appeals and succeed. One has to allow for a process of modification. Sometimes the switch is restricted in some way and we also allow for quantity, duration, interactions, back to the doctor, etc., to come in as part of the package. I think an appeal is a good way forward.

## EBERWEIN:

In Germany there is also a clearly structured procedure for Rx-to-OTC switching and the question raised by Dr Soller, i.e. if there is a negative decision, there are reasons given by the competent Expert Committee which are communicated to the pharmaceutical company. This is a recent development of the last few years. Although we do not have a formal appeals procedure, the company is free to introduce another application once the questions are answered. Most of the big switches of the last years have needed two or sometimes three applications, and there is a sometimes lively discussion between authorities and applicants. However, the procedure could certainly be improved, and I believe this is something we should work

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on. We should also improve communication and information at all levels, i.e. between company and authority. As a basic requirement, we should also work on a better education and information level of the patient / user of OTC medicines in order to get access to new indications. We think that the model requiring a first diagnosis and sometimes the first prescription by a medical doctor, a model we call "collaborative care", is a big opportunity for self-medication in the future.

**RAINE:**

There is a problem when the reason for a switch failure is a possible future development such as antibiotic resistance. How does an applicant produce a good case for an antibiotic for example that resistance will not be a problem? I think therefore that it is not just a case of iterative reproduction of data and arguments but how do you get data to answer a potential issue in the OTC environment. Antibiotics are perhaps a special example in that there has been a recommendation that they should remain prescription only. But it does relate to other problems where good data in the OTC sector cannot be captured at the moment.

**SCHOLTZ:**

Here we are talking to representatives of developed countries. The decision to switch of course also depends on the health system or health environment. If for example you ought to monitor safety and your system does not allow this because there are not enough pharmacists in the country, this would then obviously drive your decision whether or not to switch a product from prescription to OTC. I also realise with satisfaction that there is the way back from OTC to prescription, and our aim has to be to reduce the cases where inappropriate use of OTC products leads to a cost increase.

**CAMPILLO:**

I would like to comment on Dr Raine's presentation. I think it was not only outstanding but also very clear, and I share most of the criteria stated by her. In the case of Mexico, in the last four years or so we have been leaders in the area of switching. There are now 77 substances registered as OTCs, out of which 33 were approved in the last four years. We carry out constant research in trying to find out which medicines can be switched. I would like to point out that industry also has a good job to do in this respect since they can suggest to the authorities which products could be switched. Once we have proper information, we can consult academia, associations and other experts within the public sector. In this way we can move the border between prescription and non-prescription as it is a cultural phenomenon in Mexico to buy prescription products also without a prescription. Industry may thus take an important initiative in this process. However, it also needs to be very responsible. Industry in Mexico is dominated by international companies. What they promote in our country has to be consistent with what is promoted by our neighbours, mainly Canada and the United States. However, they sometimes try to switch a

product still under prescription control in the United States or Canada.

**SCHOLTZ:**

This brings us back to an earlier comment that a product classified as OTC in one country does not necessarily mean that it can automatically be OTC in another country. Obviously, there is a trend but one should see what the requirements surrounding the switch are: how can safety be monitored and how can we ensure that it is appropriately used in a particular setting.

**CAMPILLO:**

Sometimes companies' headquarters may not even be aware of these different settings. When dealing with the situation that sometimes companies are not in favour of switching to OTC status, there is something of a reverse tendency and the reason is very simple. If they have prescription-only status, products usually attract a certain reimbursement level. This may be very low, but some reimbursement exists. In case a product is switched, it loses this advantage. Therefore companies sometimes hesitate to switch particular product, especially if the population's purchasing power is relatively low.

**SCHOLTZ:**

Before moving to the next topic, advertising, patient information and trade names, I would like to state that the WHO is actually working with the agencies to come up with guidelines for the regulatory assessment of medicinal products for use in self-medication. Obviously this conference will also help us to reflect on what these guidelines should look like.

I would like to invite the next speaker to talk about trade names. You may know that some legislations require that a trade name, which we all know to represent a big asset to the industry, should be changed for whatever reasons.

**MÜLLER:**

When a brand or a category is switched from Rx to OTC, there is unfortunately only a small number of countries allowing this trade name to be used for both the Rx and OTC product. We are of the opinion that this is a big problem leading to more confusion for the consumer. We would like to ask the panel to discuss this issue on a rational rather than an emotional basis so that we can find out your real concerns behind this issue.

You may know that there was a discussion in April 1999 in the EU's Pharmaceutical Committee when the European Commission submitted an addition to the September 1998 switch guideline containing a common European regulation of this point. Unfortunately three Member States rejected this. This was in so far encouraging that we had the feeling that the majority of European countries understand what the opportunities of keeping a well-established trade name are. Maybe this discussion will help convince the three so far unconvinced countries to change their opinion.

**LINGAM:**

Would the panel agree that retaining the same brand name for an OTC product as that of the Rx product would cause less confusion and therefore lead to better safety since the consumer would already have a good understanding of the proper use of the product and its risks and benefits?

**SCHOLTZ:**

I think we should go around the table in a rational way to see what are the benefits – and there are obvious benefits – of maintaining the same trade name. We should also examine what are the risks and then maybe come to a statement about benefits and risks for the consumer.

**DEBOYSER:**

I have no problem with maintaining the same trade name for the OTC product, and that is why my service took the initiative of proposing to the Pharmaceutical Committee to enshrine this principle in the existing guideline. It so happens that the three Member States opposing this in the Pharmaceutical Committee are not represented here at the table today. As Chairman of the Pharmaceutical Committee I feel somewhat obliged to put their views.

First, I do not think anyone would argue for a change of brand name when the product is switched altogether, i.e. when all forms and presentations move from prescription to non-prescription. This is important because it shows that the only problems some regulators have is when the product remains prescription-only in some respects, i.e. only a dosage form or some indications are switched.

The problem is that in the European Union there is still a total ban on the advertising to the public of prescription-only medicines – something many European countries feel very strongly about. As you know, the European Commission is also due to revisit that ban in the coming years. The concern is that since the brand name of the self-medication products would be advertised to the general public, there would be a spillover effect on the prescription-only version of the product. Secondly, and this is certainly the main reason, the prescription-only version or dosage form is available for reimbursement. If there is advertising for a certain OTC brand name, these authorities fear that patients would go to see their doctor and ask for a prescription for that product, leading to higher reimbursement expenses. The reason is therefore basically one of cost containment.

We in the European Commission do not see that problem and I believe there is evidence to prove this. For instance, a country that was traditionally opposed to the use of the same brand name, Belgium, has reversed its policy. The first switch under the new regime was Zovirax®, and we now know that there was no increase in the number of prescriptions for this product eligible for reimbursement. The evidence we have seen therefore suggests that this is a theoretical problem more than a practical one. I should add that I have not seen a single case of

switching where there was this spillover effect increasing the number of prescriptions for a product.

The conclusion of the Pharmaceutical Committee was that this not an issue on which the last word has been said. A working party will look further into this matter and other related issues such as advertising of prescription and non-prescription products. Nevertheless I believe that there were other members around the table last April that had a problem with the requirement that a brand name can be kept.

Basically industry will have to come with more evidence showing that this is a falsely perceived problem.

**RÄGO:**

My question to the industry is how can you separate advertising for medicines using the same brand name for the prescription and the non-prescription product. This I believe is the concern of the regulatory authorities, independent of dosage, indication or form of administration. When discussing the same name, this contains in principle an advertising of the prescription product.

I would now like to present to you some reflections on the OTC advertising situation in Estonia.

**History of advertising in Estonia**

- Till 1991 advertising was prohibited
- During 1991-1996: not regulated by law(s), advertising allowed only for health care professionals by regulations
- During 1996-1998 advertising regulated by the Medicinal Products Act but OTC advertising still prohibited
- Since January 1, 1998 advertising of OTC products allowed in newspapers, journals, TV and radio
  - **The Advertising Act**
  - Respective changes in the Medicinal Products Act

**Why was OTC advertising prohibited during 1991-1997?**

- Society not ready
  - no traditions and experience
  - public opinion against
  - majority of doctors and pharmacists against
- Drug Regulatory Authorities against
  - rapid changes, massive influx of new drugs
  - lack of information in Estonian (PIL, package labelling)



## The Advertising Act (1)



- prohibits advertising of drugs without MA in Estonia, reimbursed and prescription only drugs
- advertising can be ordered only by manufacturer
- prohibits referring to tuberculosis or any other serious infectious diseases, cancers, chronic sleep disorders, diabetes or other metabolic diseases

## The Advertising Act (2)

- The advertising shall be
  - presented in a way that it could be understood as an advertisement
  - up-dated, easy to understand, containing enough information about its correct and safe use
  - in accordance with the approved SPC
  - containing drug name and INNs of its active ingredients
  - containing clear call for reading PIL and consulting with the doctor

## The Advertising Act (3)

- It is prohibited to use:
  - any state or governmental symbols (court of arms etc.)
  - references to public persons, famous doctors, scientists and cartoon figures (Mickey Mouse)
  - claims that medical consultation or surgery may not be necessary
  - difficult professional terms or non evidence based claims about the product characteristics and efficacy

## The Advertising Act (4)

- It is prohibited to use material which:
  - suggests that the effects of taking the drug are guaranteed or unaccompanied by side effects or are better than or equivalent to, those of another treatment or drug
  - suggests that the health of the subject can be enhanced only by taking the drug
  - is directed exclusively or principally at children or young people
  - could lead to an erroneous self-diagnosis

## The Advertising Act (5)

- It is prohibited
  - to give samples of medicinal products or sell or distribute items or printed matter as a method of sales promotion to persons not qualified to prescribe
  - to advertise medicinal products on video cassettes, video games, compact discs or by any other technical means
  - to have advertising on the front or back cover of newspapers or magazines
  - to have outdoor advertising, and inside or on the outside of public transport vehicles and taxis

## Liability: OTC medicines (I)

- Persons liable
  - persons who commission advertising
  - persons who distribute or produce advertising
  - persons who present, exhibit or transmit advertising
  - publishers of advertising solidarily if their activities violate the requirements for or restrictions established by the Act if not possible to ascertain separate liability as in clauses above

## Liability: OTC medicines (II)

- In case of violation of *the Advertising Act*
  - mandatory precept by competent authority exercising supervision (in case of OTC by State Agency of Medicines)
  - upon failure to comply with a mandatory precept administrative offence report will be presented to an administrative judge

## Liability: OTC medicines (III)



- Liability of legal persons
  - an administrative judge has the right to impose fines as determined by *the Advertising Act*
    - in case of repeated offence up to 100 000 EEK (7000 USD) or revoke the activity licence
    - fine up to 80 000 EEK (5300 USD) for offensive advertising or violation of advertising requirements concerning children
    - fine up to 60 000 EEK (4000 USD) for other reasons

## Liability: OTC medicines (IV)

- Liability of natural persons
  - natural persons bear administrative liability for violations of the Advertising Act pursuant to the conditions, procedure and extent prescribed by the *Code of Administrative Offences*

## Country Experience

- “WSMI strongly favours self-regulatory or co-regulatory methods and government post-publication enforcement”
- Estonia - legal background and real situation fully compliant with the statement but ...
  - “Individual self-regulation” does not work
  - “Collective self-regulation” to certain extent works - competitors are eager to find and report to the authorities violations
  - Warnings from the authorities are often ignored
  - Authorities compelled to use full range of armament

## Access to regulations

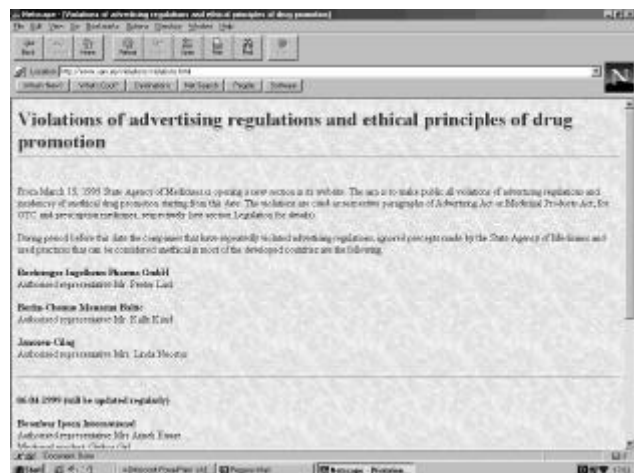
- In Estonia all major legal acts including those concerning advertising are readily available in the internet both in Estonian and in English: [www.sam.ee](http://www.sam.ee)
- What is the reason for violations if regulatory framework and advertising principles are very close to these in the EU and manufacturers are also from the EU?
  - Unprofessional approach of local representatives?
  - Poor training of local representatives?
  - Double standards of manufacturers?
  - ... ..

## Actions taken by State Agency of Medicines (I)

- **Rx Drugs.** Fines (on the basis of the *Medicinal Products Act*)
  - 1996 5
  - 1997 18
  - 1998 1
  - 1999 (01.06) 2
- **OTC Drugs.** Mandatory precepts (on the basis of the *Advertising Act*)
  - 1998 12
  - 1999 (01.06) 17
  - 1 court case coming up soon

## Actions taken by State Agency of Medicines (II)

- As mandatory precepts were not followed the authorities warned the manufacturers that the following steps will follow if the situation is not improving
  - All violations will be made public in the internet (in effect, see [www.sam.ee](http://www.sam.ee))
  - Authorities will start the administrative court procedures
  - Authorities will start in relations with the companies involved “no co-operation approach” (100% following all the regulations, time-lines etc.)



## Who is winning, who is losing

- Statement from a OTC manufacturer:
  - *Could you restore the previous situation (prohibit OTC advertising to the public)? Now we are paying more (for advertising) and we are selling more. But we are selling slightly less than we are paying, and without paying we are not selling at all!*
- Are patients winning? Probably not much, if at all.
- Is industry winning? Maybe.
- Are pharmacies winning? Yes.
- Is media winning? Certainly yes.

## Annual growth of OTC market

- Before advertising to the public
  - 1997 - + 20% (as compared to 1996)
- After starting advertising directly to the public
  - 1998 - + 27% (as compared to 1997)

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**SCHOLTZ:**

To come back to Dr Rågo's question on how you can separate advertising for medicines using the same brand name for the prescription and the non-prescription product, this relates only to the case where part of the product remains in the prescription market, not to cases where the product moves totally to OTC.

**EBERWEIN:**

I have the feeling that there is consensus that when a product is totally switched from RX to OTC, there is no problem if it keeps the same trade name. Concerning the other case, what Mr Deboyser called the spillover effect is in my opinion only a theoretical problem. In practice we have quite some experience in Germany – where the use of the same basic brand name for a switched product and the remaining Rx products is allowed – the number of prescriptions for the remaining Rx product does not increase. It usually goes down.

**JOST:**

In Switzerland, we solve this problem in the following way. It is not the regulatory authority that fixes the conditions whether a product is being reimbursed by the social security or not. This is done by the social security system itself. If a product is only partially switched from prescription and reimbursement to OTC, the product itself can choose whether it wants to remain on the reimbursement list or not. If it wants to remain reimbursed, it is now allowed to advertise. It can only advertise in the pharmacy, in a very limited way. The moment the advertising is enlarged, the social security system will remove all presentations of the product from the reimbursement list. With this system we have gained quite positive experience and the name of a product can be kept when it is switched from Rx to OTC.

**SCHOLTZ:**

So this is a trade-off. This leaves the industry with two options: either the OTC product with the same name as the product remaining in the prescription part is not advertised, or the prescription product is no longer reimbursed.

**LINGAM:**

Another dimension would be, as we have seen in some countries where the use of the same brand name for both prescription and OTC and the product rests in both categories, one way to overcome this is by identifying it with a suitable suffix or prefix. I can recognise the constraints and concerns you have about contravention of the current advertising directive. However, by definition a prescription product is a product that can only be prescribed by a doctor, and therefore it is the doctor's decision whether to prescribe or not prescribe a product based on the patient's medical condition.

**ŠMÍD:**

Maybe we as regulators contribute somewhat to the mess. Maybe the importance of suffixes and prefixes should be further stressed in the differentiation of products. We probably cannot say that Zovirax® has been switched. Zovirax ointment 2% has been switched but not Zovirax injectable. This is important to stress in the advertising v reimbursement debate.

**PAÁL:**

In Hungary the use of the same brand for Rx and OTC products is permitted. Of course it should be clear in the advertising what is to be advertised. For instance, Ranitidine® 75 may be advertised, not Ranitidine® tablets.

**SCHOLTZ:**

The legal basis for regulators' concern is very simple and has been mentioned several times already. Once you promote a brand name to consumers and there is a regulation prohibiting this promotion, this needs to be adequately addressed. This brings us back to the question to which degree we are or are not restricting the promotion of prescription medicines.

**MÜLLER:**

Mr Deboyser, what could be an appropriate way to bring the Rx and OTC brand name discussion on a more factual basis? I think there is a lot of data available in e.g. Mr Quaeys's presentation to demonstrate that there is no proof that advertising for OTC medicines will boost the remaining prescription part.

**DEBOYSER:**

I think using Aspirine® as an example is quite appropriate. In France, low-dose acetylsalicylic acid is also a prescription product for heart protection and the Aspirine brand name cannot be used for that reimbursed indication.

Now what is the way forward? I am sure AESGP will press the matter mainly with the countries most concerned. We will do it at the level of the Pharmaceutical Committee. There could be a case for including the subject in the 2001 revision of the marketing authorisation system.

When we started mutual recognition by adopting the directive in 1993, it was decided to leave legal status out of mutual recognition. Probably this was a wrong decision. The Commission had proposed to include it, but the Member States and I believe also AESGP were not in favour. Maybe they have now changed their mind.

There is moreover an issue of the free movement of goods. A company could go to court against a Member State and claim that not being able to use the brand name it uses back home would be in breach of EC Treaty Article 27 (formerly 30). I think the issue is still open. I like the solution Switzerland has adopted because in any case the paymasters of social security retain the power to dereimburse a product. In my view, rather than do it systematically – this could be the ultimate weapon if people

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believe there would be a spillover effect – one could wait until the evidence is there and then delist the product.

As I mentioned before, the Commission will set up a working party where this subject will be discussed in the Pharmaceutical Committee.

**FROM THE FLOOR – KAUFMAN:**

Would industry be interested in a solution where, if there was an increase in reimbursement because of advertising, industry would reimburse to social security excessive reimbursement? I know that in the United Kingdom has been proposed under the PPRS system as a quid-pro-quo for switching and was part of the initial arguments used there.

**EBERWEIN:**

The question is indeed interesting but on what would this be based? It should be based on evidence and the question is does public advertising lead to unjustified prescriptions by doctors. There is I believe no evidence to sustain this, even in the case where Switzerland decided to delist and in the other case where a product is only partly switched. I think that medical doctors are independent enough in all countries to write prescriptions only on the basis of a justified diagnosis.

**SCHOLTZ:**

If we accept that there is increased awareness of all forms of a product, your hypothesis is that this promotion has no effect on prescription sales. Others feel that there is an effect because it might increase prescription use of the product. The question is then, why do regulators not want to allow the promotion of prescription products? In other words, what would be the downside of promoting prescription products, and this would indirectly provide an answer to your question.

**FROM THE FLOOR – REINSTEIN:**

Mr Chairman, I think we should be distinguishing here between prescription-restricted products and non prescription-restricted products, and it should be clear in this discussion that we are speaking of non-prescription medicines even if they may be prescribed. I want to make another point, the reason that there has not been any evidence for an increase in prescriptions when a product with a similar brand name is advertised is because there is a balancing factor. Just as a doctor could decide to bow to the request of his patient to prescribe something that was advertised, he can also decide that because it is advertised he will not prescribe it so much. This is what produces the balance and why the net result is probably close to zero.

As Mr Deboyser just said, you can always tell a manufacturer that if a switch is going to result in more reimbursed prescriptions, you can dereimburse it. The industry has to be willing to take that risk.

**RAINE:**

I do not know whether this comment will help but we have clear EC law on advertising. Our interpretation of that law in the UK is that if a brand name is used for an OTC which is also in the prescription sector, that is not an advertisement. In a sense this could be a legal matter. We would not consider that there was a breach of the advertising law by a product such as for example Beco-nase® and Beconase Hayfever®. We would not be able to enforce that legally.

**RUDAKOV:**

When listening to this discussion I was very surprised. Because you have to take into account that this problem with brand names in Russia does not exist. Or maybe it is a problem, you can judge for yourself. There is for the moment no reimbursement of prescription medicines in Russia, so they do not cost the government any money. Another reason is that it does not matter whether it is a prescription or a non-prescription medicine because you may go to any pharmacy or any kiosk to buy any medicine you want – even an anti-tumour product – without a prescription – if you have money. Another reason is that unfortunately in Russia you can now find advertising for ethical or prescription drugs like for non-prescription medicines. Maybe this will be resolved in the near future.

**DEBOYSER:**

One last word. When you prepare for that discussion, you must realise that there is a different culture in countries such as Spain, Portugal, Greece, Italy and France. When you say that there is no spillover effect, I agree that this has not been the case in Germany, in the UK, in the Netherlands or in Denmark. However, are you sure that there would not be one in a country like France, which has a definite problem of volume consumption? This is why I thought the Belgian example was very useful. Belgium for that purpose rather belongs to the Mediterranean countries, as it is a high-volume country with traditionally very strict advertising restrictions and a change-of-name policy. However, this policy was changed without any particular problem.

I therefore think that you have to prepare in the context of these countries. Do not just say that there is no problem in the UK, a country with a rational prescribing scheme not found in France, for example.

**EBERWEIN:**

I would put the question the other way around. We know that there is a no spillover effect in some countries and my question is, is there evidence that there is a spillover effect in France?

**DEBOYSER:**

You will not find this out until the situation arises. You will have to convince the French authorities, not me. I am already convinced. I am just telling you to prepare for this discussion.

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**PAÁL:**

I would like to answer Dr Eberwein. I am not on very good terms with the Hungarian social insurance bodies. However, at this moment I think they may be right in saying that there may be a spillover effect and that they may lose a lot of money. Who will compensate them for this if it occurs? So they do not take the risk.

**SCHOLTZ:**

Obviously each regulatory authority will have to evaluate which risk if any it is prepared to take. There is also the question of whether this issue should or could be further investigated. I we could agree on a common protocol, more evidence could be added towards a final policy. Maybe WSMI and WHO could also look at this in the framework of the further collaboration on outstanding issues, including advertising, agreed a couple of days ago at our roundtable.

**VECINA NETO:**

Public health comprises an intricate number of actions to protect, promote and recover people's health with the objective of improving their living conditions, or, in other words, to make human life on earth take a turn for the better. These actions cannot be isolated but are closely interconnected with other sectors.

In developing countries like Brazil, which face many structural problems such as providing housing and education and guaranteeing employment, public health has to compete for resources with many others areas. Moreover, these countries are confronted with a new environment that could be summarised in the following points:

- The demographic revolution – an increase in birth rate coupled with a reduction in mortality and the resulting increase in life expectancy have had important consequences for the number of health services and actions used.
- The epidemiological revolution – apart from the existing infectious disease pattern that is far from been resolved, a new degenerative disease pattern is emerging with diseases such as AIDS while others such as cholera and dengue fever are re-emerging.
- The technological revolution – the addition of new technologies and new processes on top of existing ones continues to create an unending cost spiral in the healthcare system.
- The information revolution – health professionals and citizens have forever better access to information, turning them into providers / consumers with unprecedented power of decision. They are then faced with centralised and anachronistic organisational solutions generated by inefficiency. Besides an increasing wish to see their health needs satisfied, these providers / consumers also need quality solutions.

This equation leads to an explosive situation – leading to inequities and low quality.

What can we do when faced with this very simplified framework? There is consensus that we have to break

with the classic image of the physician controlling all the knowledge to come to a situation where knowledge is shared. This means that we have to give more attention to promoting health strategies or, in other words, that we have to turn citizens into promoters of their own health.

In parallel, we have to reinforce inter-sectoral strategies, in particular in the social area as suggested in the "Healthy Cities" movement. In the healthcare sector, we should develop a series of procedures to make healthcare more efficient and guarantee every citizen access to it. One example of this trend is the development of "Managed Care"; i.e. the creation of public bodies independent of state control – new transparent healthcare entities – using management tools that are classically found in the private sector.

However, the question is not only to reduce costs but also to become more efficient in order to achieve our organisational goals.

On top of these inter-sectoral strategies comes the political question of providing good quality medicines. This could be briefly explained as increasing the population's access to quality medication (therapeutic efficiency). In this specific area, what we get today is unstructured healthcare assistance and at the same time an absolutely unorganised market with an enormous set of hypocritical rules. The market offers a great number of options, more than are necessary in the name of free competition and free market policy, without taking into consideration the population's real needs and the system's accessibility.

On the other hand, the government's regulatory actions are limited to certain framework measures which lead to incomplete records, provide inadequate management information and do not allow the government to resolve possible problems. This is the worst of all worlds – on the one hand we have enterprises wanting to make a profit and not recognising their social function, and on the other we have an incompetent government system.

While agreeing that this picture could seem too much of a caricature, it is at least informative and shows us the strategies of both sides. We all want a better world in which to live and make money.

We are talking about increasing information for citizens and turning them into knowledgeable consumers. We are talking about creating a competitive market where it is possible to see prices fall and access increase. The state should use all the necessary tools to steer and regulate policy in a way to guarantee access to healthcare for people on the fringe of society and ensure quality products are available to the citizens at large.

We are not dealing with a utopian or Cartesian vision of history. We are not wavering in our policies but are here to build a strong agreement between industry and the State to achieve these goals. This means the creation of a better market and the introduction of a new approach to the entire public health system, not only concerning medicinal products. We could even say that this approach is more complex to achieve in a decentralised than in a centralised country.

With the aim of developing the promotion of responsible self-medication, Brazil is for the moment, together with the pharmaceutical companies, reviewing the OTC

categories and monographs. The legislative moves to achieve this are in the first phase. However, reaching the customer through an adequate selling network with ethical marketing strategies will be much more difficult. Moreover, taking into account all the questions mentioned before, we are not looking only at the OTC market segment but at the entire pharmaceutical market. This kind of vision must be accomplished together: both industry and government should fine-tune their opposing interests and converge towards a common goal, to the benefit of the citizens.

## ŠMÍD:

### Rational use of medicines

I have prepared some general statements but would like to raise some issues derived from that. What we see in the regulation of rational use issues is a major progress from the assessment based on tradition and some regulatory culture through the economic interest overcoming political pressures and lobbying and finished with evidence-based decisions. In the area of classification and switches, maybe we are at the level where we really take our decisions based on evidence. But in the other areas this is less pronounced. In the area of advertising, a lot of data are still missing. What is the real impact on public health, on the use of a medicinal product? The same goes for the use of trade names, umbrella brands, etc. We simply deal with some presumptions but often lack the data.

#### *Rational use*

- **Classification for the supply**

Risk/benefit concerning availability of medicinal products and qualification of professionals in distribution channel

- **Labelling / Package leaflets**

Risk/benefit concerning completeness, correctness, understandability and legibility of user instructions

- **Advertising**

Risk/benefit concerning truthfulness of core message on the product

- **Trade names**

Risk/benefit concerning mix-ups and misuse

#### *Approaches to regulatory decision making*

- Tradition? Ethics? Regulatory culture?
- Economic interests? Politics and lobbying?
- Evidence based decision?

#### *"Rational use" and CEECs*

- **Major social and economic changes**

- Trust in pharmaceuticals
- Traditional respect to medical professionals
- Value of health identified
- Value of money identified

- Improved self-responsibility
- Susceptibility to advertisement
- Break down of information barriers
- New information technologies
- New "user friendly" indications of medicinal products (sexual disorders, alopecia, obesity, psychic stress disorders)
- Privatisation of distribution channel
- Economic constraints of public health expenditures
- Development towards EU regulatory environment
- Overloaded regulatory authorities

#### *Classification for supply*

- Directive 92/26/EEC on classification for supply
- Notice to Applicants Vol. 2A, Chapter 6, part 5
- Guideline on changing classification for supply  
Based on submitted data
- **Local issues to be considered**
- Awareness of self-medication (acute/chronic diseases)
- Self-responsibility
- Compliance with labelling/leaflet information
- Experience with OTCs
- Role of medical doctor and pharmacist

#### *Distribution channels*

##### *General Sale Lists*

- Added value of pharmacy retail in comparison with risks of daily life and free availability of alcohol, nicotine, caffeine, sushi (and addictive substances)?
- Is the service of pharmacy worth 25% of the price of a medicinal product?
- Whose opinion is reflected in decision making on GSL?
- Decisions based rather on tradition, politics, lobbying, economic interests than on risk/benefit data

#### *Labelling / Package leaflets*

- Directive 92/27/EEC on labelling and package leaflets
- Notice to Applicants Vol. 2A, Chapter 6, parts 3, 4, 6
- Guideline on readability of the label and package leaflet
- Guideline on excipients in the label and package leaflet
- **Local issues to be considered**
- National and lay language
- Acceptance of instructions
- Involvement of patient groups judgement in the decision making process and during refinement of

information

- Focussing on important instructions supported by the advice of medical professionals

### ***Warning of Minister of Health:***

- Beware!  
Drinking beer causes headache!

### ***Advertising***

- Directive 92/28/EEC on advertising
- WHO ethical criteria for medicinal drug promotion
- WHO ad hoc Working Group on cross-border advertising, promotion and sale of medicinal products through Internet
- Impact of electronic commerce on the European pharmaceutical sector
- ***Local issues to be considered***
- Susceptibility to advertising
- Compliance of adverts with approved product information
- Availability of data on impact on the public

### ***Trade names***

- Single name for medicinal products authorised by the Community - Pharmaceutical Committee working paper
- CPMP guidance paper on the acceptability of trade names (centrally authorised products)
- Commission communication on the Community marketing authorisation procedures for medicinal products
- Commission communication on single market in pharmaceuticals
- Subjective view on risk of misinformation and misuse
- ***Local issues to be considered***
- National language and existing trade names of medicinal products
- Relative risk of causing confusion

### ***Needed?***

- Common definitions/practice in classification of borderline products
- Evidence based decisions on "rational use" issues
- Common regulatory standards/ guidelines (ICH?)
- Decisions respecting national environment and view of "customers"
- Regulatory procedures on "rational use" more transparent and predictable

Of course there is the local culture which must be taken into account when dealing with individual coun-

tries. There are many issues which must be identified here as having a role: the socio-economic structure and the structure of the public healthcare system just in pharmaceuticals, low-volume and high-volume countries, respect for medical professionals, and many other issues.

What can be seen as major progress in the last years on all these issues is in principle that some generally accepted guidelines and papers have been published? These issues were raised not only in a couple of directives which have now been projected in the countries of Central & Eastern Europe but also in the areas where standards were missing, i.e. in the area of trade names and advertising.

In summary, I feel that one of the issues needing to be resolved and not mentioned today is what should be classified as a medicinal product. This is critical issue which may in future be close to the heart of Mr Deboyser. There are plenty of borderline products and there remains the critical decision if the risk / benefit is on the side of medicinal products or not. Maybe we should try to find some common guidelines on this issue.

There is also the role of customers, i.e. the consultative role of customer groups, patient groups, etc. in decision-making procedures and their role in establishing standards.

The transparency of the decision-making process is another issue that needs to be addressed, with clear identification of the reasons on which the decisions are based.

All these issues are very complex and demanding, and are facing limited capacity of the regulatory agencies. Therefore careful prioritisation of the issues is needed.

### **SCHOLTZ:**

Classification was already discussed earlier today. I is my understanding that while the guiding principles are broadly agreed, it comes down to individual decisions of each regulatory authority how a medicinal product is classified in their environment as prescription-only or OTC. These authorities also have to decide what are the mechanisms to ensure that, while you move along in the OTC part, particularly safety is closely monitored.

One of the concerns of the industry is also the question of umbrella branding. Just to get people's minds set right, I would like to make it clear that we are talking about the OTC sector only, and the key question is what is the regulators view with regard to umbrella branding and what are the criteria. It is from the previous discussion very obvious what the benefits of a brand name are, but what are the limits and how can we overcome them.

### **FROM THE FLOOR – RAPAZZINI:**

I am Piero Rapazzini now from Brazil but originally from Italy. Creating a new brand is so expensive for the industry that there is the trend in many industries to use the same brand for products in the same therapeutic area with different active ingredients. In this case it is not so much a case for the consumer of recognising the active ingredient (the consumer knows very little about active ingredients anyway), but of relating a particular brand name to a need. For instance, in case of a sore throat or a blocked nose, one can use the same brand name with ap-

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appropriate suffixes or prefixes to let the consumer know what the product is for. What is the opinion of the regulators on this point?

**JOST:**

Of course we knew about the EU's plans to provide guidance on the use of trade names and we, the Swiss authorities, tried to be a little more flexible and have allowed, since 1997, products that do not have the same active ingredients under the same umbrella. The first principle is that there is no danger to the consumer in terms of misspelling or confusion, and the indication has to be relatively narrow, i.e. products for the nose, for the ear, for the face, for the foot, etc. Not too many thinks can be put under one umbrella. In case of a so-called cosmeceutical line, this is permitted? It also makes sense to us because the consumer is then aware that these products are all for one single and rather narrow indication.

The last two years have not brought that many new products to this umbrella solution. However, we have had no problems and there have been no reactions from the consumer that we are going too far and that the information is not sufficient as to the nature of the product.

**PAÁL:**

We have just come across this question in Hungary. When the indication is the same, the use of an umbrella brand could be discussed. However, there was a request to use an umbrella brand for different indications, and we decided to turn down this request. We did so to avoid a situation whereby, in the same family, one member is coughing and another member has constipation, and they are mixing up products because they have the same brand name. We therefore do not think that we should permit the use of too wide umbrella brands.

**MÜLLER:**

We have learned and heard so many things during the past three days concerning responsible care and the responsibility of the consumer. We know from research that the consumer deals very carefully with medicinal products. We do not really apply for one umbrella from the foot to the head because this does not make sense from a business point of view. The only thing we would like to do is giving the consumer those kinds of products with which they are already familiar. As an example, there are various ranges of analgesic brands across Europe which are already used in the area of common cold. Research shows that sometimes the pharmacist also recommends a single analgesic brand when a consumer comes into the pharmacy asking for a remedy against nasal congestion or cough. Therefore we manufacturers do not see any risk for the consumer in the use of umbrella brands.

A new point in this discussion is the risk for us manufacturers. If the responsible manufacturer builds up the goodwill of a brand over many years at a cost of a great deal of advertising money, he will use this asset very carefully. I do not think that he would consciously take the risk of misleading the consumer.

**DEBOYSER:**

I do think you spend too much money on promoting brands. However, I think the main problem is that you have been very effective in promoting the brand name rather than the common name and therefore the man in the street does not know what is behind the brand name. How many consumers know that Viagra® means sildenafil or that Valium® means diazepam, etc.? The problem is that now you want to move from there and use this name which for the consumer means the product for another product. You then probably have to abandon this promotional policy of calling a substance by its brand name. I believe that WHO has a very valid policy in promoting common names more and more, especially if you develop a policy of using a brand name to no longer designate a substance but rather a family of substances. The reason why you are doing this so effectively is that you hope – and it has worked – that when the substances come off patent people will keep looking for the brand name rather than the substance. Having come so far, maybe you should be very careful before moving into the next stage.

In the EU, the UK is the only country which is so far authorising umbrella brands. I would like to know whether the experience in the UK is positive.

**MARTINEC:**

According to our law, it is theoretically possible to register an umbrella brand as there is no prohibition that a brand name should be directly connected to the active ingredient. However, I agree with Professor Paál that if there is one brand name for different indications, this could cause some confusion for the patients as they have been used to a particular brand name being associated with a particular indication. I understand industry's wish to use well-established brand names as this is less costly and could promote sales. However, I believe we should be very careful how to deal with this issue.

**RAINE:**

Historically, the use of branding is a very ancient tradition in the UK. PAGB is 80 years old and some of the products in the market, e.g. Beecham's pills, are maybe 100 years old. The issue of brand loyalty is something the industry will speak to. From the regulators' point of view, we have to be clear that our responsibilities are for quality, safety and efficacy. The UK policy such as we can justify and rationalise it is that if a brand name of a medicine is strongly identified with a particular ingredient, and if confusion with another ingredient would cause a risk to public health or patients' safety, we would refuse that, and we have.

From the regulators' point of view it therefore has to be a safety issue but the UK perspective is a pragmatic one because many of these old remedies have a tremendous loyalty among members of the public. We do operate informal guidelines that help us to make these decisions, but at the end of the day when we refuse an umbrella brand name, it is on grounds of safety.

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The only other aspect to bring up which will perhaps link up with our next debate on good product information is that we insist that the labelling of umbrella products containing different active ingredients is particularly clear and effective on this point. Modern techniques of presentation can be very important in the labelling and packaging of these products.

**FROM THE FLOOR – ZANIBELLI:**

My name is Angelo Zanibelli. I am Vice-President of Assosalute, Italy and country manager, Sanofi Synthelabo OTC. The situation in Italy and the position of Assosalute are as follows. We propose:

- to limit the extension of umbrella brands to the same therapeutic area
- to use a denomination after the umbrella brand that clearly explains the application of the product.

We believe that the use of umbrella brands is one of the few keys to develop the OTC market. As Mr Rappazzini mentioned before, to launch a new brand is very expensive. In limited markets it is impossible to launch a new fantasy name each time a new product is launched.

Other important points are quality and safety. If I use a brand name with a big awareness and I apply this brand name to a product that is not effective, this is very dangerous and I risk affecting the main brand negatively. There is also a warranty for the public authorities that I am obliged to develop a product with a maximum of quality and safety.

The risk of confusion for the end user we are trying to solve with a name that clearly indicates the application of the product. Before the end of the month we will have the results of a consumer market survey in which we have found that the end user asks for an OTC with a clearly identifiable brand name. This brand name is considered as a kind of signature or warrant that the product is a known, safe and effective product.

We have been discussing this position for many years with our authorities. The situation in Italy on this point is extremely confused and unregulated, and the decisions can be different from one minute to the other, based on the mood of the day.

**FROM THE FLOOR – KAUFMAN:**

We are talking here about marketing companies that are putting products on the market after having tested them, to make sure that the brand can support the additional use of the product or the additional indications. They have that data in all cases because if they are not testing they are taking a great risk. My question for industry is, are you presenting that data to the regulators when applying for umbrella branding?

**FROM THE FLOOR – YONG KWOK:**

I am here in the capacity as co-chair of the Labelling Dialogue Group but I have also worked for a number of years as a researcher and policy maker for national consumer organisations. I just want to make a couple of comments and observations from this morning's proceedings.

One is that there a lot of assumptions are being made about what consumers want and think. Reference has been made to market research work carried out. Sometimes you get answers depending on what kind of questions you ask. There is also an advantage in consulting consumer organisations because they are able to generate these sort of issues into policy positions, what you are doing here. I think it is excellent that industry members are able to get together with regulators to discuss policy issues.

In a number of countries, there is a movement towards greater consultation with different stakeholders, e.g. in the United States. It also takes place in Australia, where members of the consumer organisation are involved in scheduling committees and other drug evaluation processes. My suggestion to you is that there is perhaps a need for regulators around this table and around the world to look at ways, despite your limited resources, of how your local consumer or patients groups can be involved, as appropriate, in these policy discussions. You may not want to extend that to specific medicinal products which have data that are held in confidence, especially concerning new products. However, in terms of policy issues, this sort of forum ought to be extended to consumer organisations.

Our consumer organisations have always asked that we be educated on the common names of products. To always have brand names and not be informed about common names does not allow you to make comparisons, especially when it comes to self-selection.

**SCHOLTZ:**

I think that this was an excellent summary. Whatever we do with regard to policy making and patient information, we always have to bear in mind who is the consumer, what are his or her needs and how can we make sure that he/she receives the medication needed in a safe and effective way.

I think this morning's discussion was very helpful to get different ideas and different things to reflect on. I thank you very much for your lively participation.