行政院及所屬各機關出國報告

（出國類別：考察）

赴歐洲考察指示藥品及成藥管理

行政院研考會/省(市)研考會編號欄

服務機關：行政院衛生署藥政處
職　　稱：科長
姓　　名：劉麗玲

出國地區：英國、德國
出國期間：九十二年九月三十日
　　至九十二年十月九日
報告日期：九十三年一月

公 務 出 國 報 告 提 要

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報告名稱:

赴歐洲考察指示藥品及成藥管理

主辦機關:

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出國類別: 考察

出國地區: 德國 英國

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分類號/目: J0／綜合（醫藥類） J0／綜合（醫藥類）

關鍵詞: 處方藥，指示藥，成藥

內容摘要: 目的：目前我國指示藥品及成藥市場佔所有藥品市場之比值較歐、美、日國家偏低，為促進產業經濟及增進民眾用藥便利性，增進醫療照護有效經營，宜擴大該市場，此次考察有助於了解與我國藥品分級(處方藥、指示藥、成藥)相類似而市場大之英、德先進國家管理制度，以為本署訂定政策參考。 我國製藥業現仍以生產學名藥為主，而台灣市場狹隘，業界抱怨經營困難，面對現今知識競爭，保護智財權之觀念及發展高科技產業之全球趨勢，我國製藥產業須有研發新藥能力，惟研發新藥耗費資金龐大，故除鼓勵產業界整合減少資源浪費外，另擴大學名藥市場，以增加營業利潤，始有經費進行研發投資，另指示藥／成藥市場不受健保給付影響，應是我製藥業努力的方向。

摘要

目的

目前我國指示藥品及成藥市場佔所有藥品市場之比值較歐、美、日國家偏低，為促進產業經濟及增進民眾用藥便利性，增進醫療照護有效經營，宜擴大該市場，此次考察有助於了解與我國藥品分級(處方藥、指示藥、成藥)相類似而市場大之英、德先進國家管理制度，以為本署訂定政策參考。

我國製藥業現仍以生產學名藥為主，而台灣市場狹隘，業界抱怨經營困難，面對現今知識競爭，保護智財權之觀念及發展高科技產業之全球趨勢，我國製藥產業須有研發新藥能力，惟研發新藥耗費資金龐大，故除鼓勵產業界整合減少資源浪費外，另擴大學名藥市場，以增加營業利潤，始有經費進行研發投資，另指示藥／成藥市場不受健保給付影響，應是我製藥業努力的方向。

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貳、過程

9月30日

起程赴英國倫敦

10月2日

拜會英國 OTC 藥品公會(Prprietary Association of Great Britain; PAGB)

受訪人員：Sheila Kelly,

Execution Director

10月3日

拜會英國衛生主管機關(Medicines and Healthcarevproducts Regulatory Agency, MHRA)

受訪人員：Miss Shirley Norton,(Group manager,post-Licensing

Assessment)
Mr. Jeremy Mean (Senior Policy Manager, Post Licensing Division)
Mrs Amanda Williams (Legal reclassification Manager,
Post-Licensing Dirision)

10 月 6 日

拜會德國藥品公會(BAH, German Medicines Mannfacture Association)

受訪人員：Dr. Rose Schraitle (Director), Dr. Uwe May

Dr. Ehrhard Anhalt, Dr. Elmar Kroth.

10 月 7 日

拜會德國衛生主管機關(BfArM, Federal Institute for Drags and Medical Devices)

受訪人員：Dr, Peter Bachmann (Head of Unit "Mutual Recognition products")
Werner Knoss (Unit Pharmacentical Assessmant of Herbal Medicinal Products and Traditional Medicinal Products)

10 月 8 日

回程。

德國非處方藥管理

1. 分類管理

(1) 德國的藥品分類：處方藥 (prescription-bound)、指示藥 (Pharmacy only)、一般通路可賣 (sold outside pharmacy)，所以一般口語所說的 OTC 包括 Pharmacy only 及 sold outside pharmacy。

(2) 德國藥品的管理觀念是：依藥事法規定在一般的狀況下，藥品應是在藥局不需處方即可販賣 (German drug law: Medicinal Products are generally prescription – free and sold in pharmacies only.)

pharmacy only 放置於藥師櫃檯背面，即需藥事人員監督。

(3) 上述原則為基礎，例外的情形如下：

prescription-bound

a. 新藥 (新成分、新使用途徑、新適應症)

b. 列於處方藥的正面表列中 (一般皆考慮使用的安全性應有醫師監督)

general sale (sold outside pharmacy)

a. 作為預防使用

b. 列於正面表列中 (個案申請增列)

2. 藥品給付

(1) 社會法要求藥品應該要給付，但依國家財政、產品品質及適應症之不同嚴重程度來訂定藥品之給付方式，有正面表列。

(2) 所以處方藥有給付外，部分 OTC 也有給付

(3) 但自 2004.01 開始，健保新制開始實施，強制只有處方藥始可給付，如此以來，影響原有被給付的 OTC 之經營，目前有些 OTC 企圖申請再分類為處方藥以維持其醫院市場，但所有分類是藥政處做最後的決定，預估將有 1/3 的被給付的 OTC 會受影響。

3. 藥品類別 Switch 的環境

(1) 因德國政府原先就鼓勵藥品是以非處方藥的方式販賣，一般若處方藥在市場行銷五年以上，廠商可蒐集相關安全資料來申請再分類 (Rx-to-OTC switch)。

(2) 再分類的評估主要是著重藥品的安全性 (risk assessment)，而不考慮其給付的問題。

(3) 再分類的申請重點，除一般的技術性文件外：

a. 申請的資料能說明可自我醫療的適當性 (adequate for self-medication)：說明病人是否有能力作自我診斷，即

症狀很明顯，如：感冒藥

b. 病人是否有足夠的知識判斷用藥禁忌，產品副作用之嚴重性，是否容易被誤用。

c. 如果有同一商品或同類商品使用於自我醫療的經驗 (有時是 clinical study，有時是用一個正式的 market survey)，可作為申請的支持文件。

d. 包裝標示應以消費者易懂的文字表達。

(4) 對於第一家分類成功者雖無 exclusivity，但可讓其在廣告上宣稱其為第一家。

4. 產品登記

(1)處方藥與非處方藥並無不同的方式，且 GMP 或化驗的要求亦相同。

(2) 我們曾針對複方做確效及安定性試驗要求向德國請教，但因德國的複方成分至多二至三種，所以都還是與單方的要求一樣；唯有 herbal medicines 在加速試驗的要求較鬆。

(3) 維生素製劑在德國多為 food supplement 大多不在藥品的管制中，目前 EU 正在針對維生素製劑進行整合，包括限量及品質要求，但尚未有結論。

5. 廣告

(1) 廣告有相關的法規來管理。

(2) OTC 藥品可在大眾媒體廣告，不需事先申請。

(3) 監督機制：

a. 地方衛生單位查廠時有時會一併檢查

b. 藉由廠商自律的機制，若有太過誇大的廣告其競爭品會檢舉。

6. 消費者教育

(1) 公會除了在整合業界的意見及與政府溝通外，同時在消費者教育扮演一個重要的角色，包括 TV report (公益廣告)。

(2) 業界也會有教育宣導手冊同步提昇民眾用藥知識。

7. 市場

(1) 市場金額比

	金額 (Mrd. EUR) (十億歐元)	Share (%)
處方藥	25.74	78
給付的 OTC	2.93	9
自我醫療的 OTC	3.87	12
General sale	0.33	

(2) 市場量比

	數量 (Mio)(百萬單位)	Share (%)
處方藥	725	44
給付的 OTC	278	17
自我醫療的 OTC	560	34
General sale	84	5

英國非處方藥管理

英國面積：243,820 km^2 ／人口：60109410／健康照護費用：euro 80.56 billion (5.2%of GDP)

1.產品分類：

I. Prescription Only Medicines (POM)
II. Pharmacy Medicines (P), behind the counter.
III. General Sale List Medicines (GSL), can be sold out of pharmacy.

2.產品登記：

各類產品管理皆須辦理產品登記，維他命類產品皆以食品列管，但不能宣稱藥品適應症。

3.市場資料：

市場有 17000 種產品(其中 P+GSL 產品佔約 25%)，非處方藥市場金額：euro 3557.5 millions(約佔全部藥品市場之 24%)

4.產品標示：

產品標示須符合 EU Community Code，歐盟有公佈新 labelling guidelines 可上網查詢。

5.廣告管理：

P 或 GSL 可產品廣告，但不可做為贈品促銷，藥品公會(PAGB)依"Code of Practice of Advertising" 負責審核廣告。

6.Switch 原則(考量因素)

(1) the hazard to health,
(2) the risk of misuse, or
(3) the need to take special precautions in handling are small, and
(4) where wider sale would be a convenience to the purchaser.

7. Switch 申請案應檢附資料

(1) Reclassification Application Form
(2) Reclassification Summary
(3) Safety/Efficacy Summary
(4) Patient Information
(5) Training and Education
(6) Clinical Expert Report

參、心得

一、推動 Self-Medication 之優點如下：

(一)減少保險給付負擔

(二)增進民眾用藥便利性(例如超商營業時間較藥局長)

(三)增進藥師及民眾藥學知識教育

(四)促進製藥產業經濟

二、我國應英國、德國之比較：

(一)現況分析：

我國係採四級制國家(處方藥、指示藥、成藥、乙類成藥)，乙類成藥可於超商販售。英國、德國、日本均採三級制國家「Prescription、Pharmacy only、General Sale List (GSL)」，GSL 可於超商販售。美國係採二級制(處方藥、指示藥)，指示藥可於超商販售。我國目前已修訂成藥基準中，未來改採三級制。

(二)市場銷售額統計表

市場銷售額	我國	英國	德國
處方藥	約 89%	約 76%	78%
指示藥	約 11%	約 12% (Pharmacy only)	21% (Pharmacy only)
成藥			
乙類成藥		約 12% (GSL)	1% (GSL)

(三)許可證核發情形統計表

許可證張數	我國	英國	德國
處方藥	18919	12750	25110
指示藥	7654	2125 (Pharmacy only)	6062 (Pharmacy only)
成藥	428		
乙類成藥	46	2125 (GSL)	484 (GSL)

(四)審查管理制度

1.上市前管理：

英、日、德均採上市前審核(preapproval)，GMP 標準對所有藥品(包括處方藥、指示藥等)是一致的，美國若符合 OTC monograph 產品係採 Annual report 制，無須 preapproval。

2.上市後管理：

(1)廣告管理：

英國：由其 OTC 公會負責審核，訂有完善廣告基準，採事前審核制度。

德國：無須事前審核，訂有完善之廣告法規，採事後查核制。

(2)ADR：民眾可向廠商或醫療專業人員通報，另

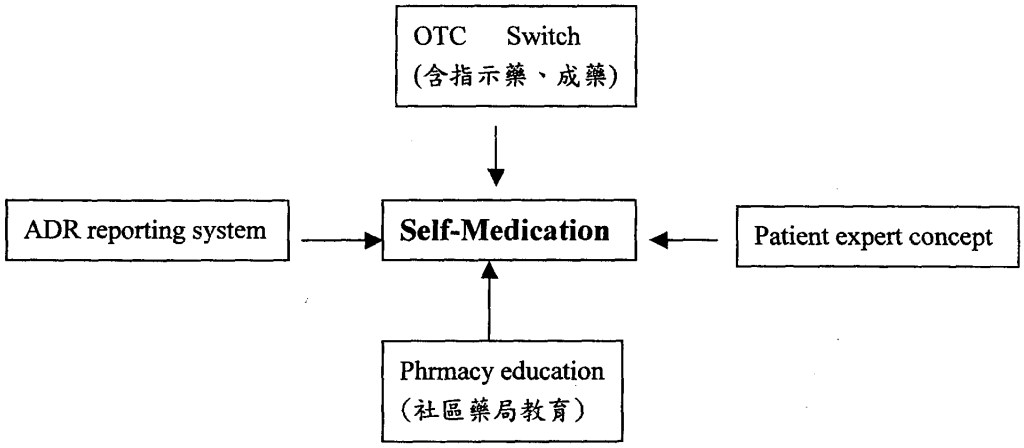
英國：可藉由 NHS program 上網通報。

德國：依法廠商須聘有專人負責 pharmacovigilance 且訂有 personal liability

肆、建議

一、 我國可參採英、德二國制度由下述方向著手，健全藥品再分類法規，加強民眾用藥知識，增進社區藥局藥事服務以及健全副作用通報系統。另二國產業自主性管理強，其公會充分發揮專業技術輔導，及廠官學三方協調功能，值得我國學習。

依下述架構 Self-Medication (指示藥／成藥)



二、 加強 Self-Medication 藥學知識教育，可透過媒體、網路、社區藥局.....等。

三、 健全廣告基準，使業者能做適當的廣告，增進民眾對藥品的認知。

四、 修訂指示藥／成藥基準及訂定藥品類別 Switch (處方藥→指示藥，指示藥→成藥)原則。

五、 仿英德, OTC 審議會由衛生機關、製藥公會、藥師公會、醫師及學者專家代表組成。

六、 英、德之 OTC 公會專業水準很高，協助廠商訂基準及各項技術輔導工作，經費均來自產業界，我國公會多為一般行政事務人員應提昇專業水準。

伍、附錄

一、A Guideline on changine The classification for The supply of a medicinal product for human use. (European Commission)

二、Law on Advertising in the Healthing Care System.

三、Traditional Herbal Medicinal Products Directive (Adverse Reaction Reporting System)

四、Economic and Legal Framework for Non-Prescription Medicines.

書籍：

一、Code of Practice of Advertising Over The Counter Medicine (PAGB 1998 Edition)

二、OTC Directory 2003/2004 (PAGB)

EUROPEAN COMMISSION
DIRECTORATE-GENERAL III
INDUSTRY
Industrial affairs III: Consumer goods industries
Pharmaceutical products

c:\data\gdlines\switch\final.doc

29 September 1998

A GUIDELINE ON CHANGING THE CLASSIFICATION FOR THE SUPPLY OF A MEDICINAL PRODUCT FOR HUMAN USE

Timetable:-

14 February 1997	Discussion of draft 1 at the Ad hoc working group on legal status
21 May 1997	Discussion of draft 2 at the Ad hoc working group on legal status
June 1997	Draft 3 approved by the Pharmaceutical Committee for release for 6 months consultation to interested parties
June 1997	Released for 6 months consultation to interested parties
June 1998	Final draft approved at the Ad hoc working group on legal status
September 1998	Final adoption of the guideline by the Pharmaceutical Committee
January 1999	Proposed date for coming into operation

This guideline will be included in The Rules governing Medicinal Products in the European Community Volume IIIB: Guidelines

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Introduction

Legal framework

Council Directive 92/26/EEC[1] "Concerning the classification for the supply of medicinal products for human use" states in the preamble that the supply of medicinal products for human use to the public varies appreciably from one Member State to another, whereas medicinal products sold without prescription in certain Member States can be obtained only on medical prescription in others. It also states that it is appropriate, as an initial step, to harmonise the basic principles applicable to the classification for the supply of medicinal products in the Community or in the Member States concerned.

Article 1 of Council Directive 92/26/EEC provides two classifications for the supply of medicinal products for human use in the Community :-

- "medicinal products subject to medical prescription"
- "medicinal products not subject to medical prescription"

Article 3 provides the criteria for classifying a medicinal product as subject to medical prescription. Thus a medicinal product which meets these criteria is subject to a medical prescription and a medicinal product which does not meet these criteria is not subject to a medical prescription.

Therefore, the criteria in Article 3 have been used as a basis for this guideline. This guideline will not address the different restrictions which may be available for medicinal products not subject to a medical prescription, such as: available in pharmacies only following initial medical diagnosis or available on general sale, as the case may be.

Purpose

This guideline is for use by marketing authorisation holders applying to change the classification for supply of a medicinal product. It is also for use by competent authorities to facilitate harmonisation, within the EU, of medicinal products restricted to medical prescription and of medicinal products available without a medical prescription.

This guideline is divided into two parts:-

- Part 1 concerns the criteria for classifying a medicinal product as subject to medical prescription or not.
- Part 2 outlines the data requirements for an application to change the classification for the supply of a medicinal product from subject to a medical prescription to not subject to a medical prescription.

[1] O.J. L 113, 30.4.1992 p.5

PART 1

Criteria for classifying a medicinal product as subject to a medical prescription or not and how to determine if a medicinal product does not meet these criteria and may therefore not be subject to a medical prescription

1. First Criterion

Medicinal products shall be subject to medical prescription when they are likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision

In considering whether this criterion applies, the following factors should be addressed

1.1 Direct danger/safety profile

(a) A direct danger, when the product is used correctly, (according to the patient information), encompasses toxicity, interactions and adverse reactions. A medicinal product not subject to a medical prescription should have:
- low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties;
- low risk of serious type A[2] adverse reactions in the general population.
- very low risk of serious type B[3] reactions;
- no interactions with commonly used medicines which can produce serious adverse reactions, [see also 1.5 c) on page 5].

(b) The criterion of danger can take account of the possibility of preventive action. For example, serious type A reactions can be acceptable if there is a clear identifiable risk group that can be excluded even in the absence of medical supervision.

(c) The safety of a medicine is always relative to that of the alternative treatment.

1.2 Indirect danger/safety profile

(a) An example of indirect danger, even when the product is used correctly, that is to say used according to the patient information, would be where symptomatic treatment might mask/hide an underlying condition requiring medical attention and supervision. Use of the medicine might delay diagnosis and definitive treatment and jeopardise the chance of more successful therapy. Package leaflet and or label warnings may be necessary to prevent treatment from "masking" the development of a serious disorder. Therefore, such warnings should indicate a time limit beyond which, if symptoms persist, medical advice should be sought. Medicinal products not subject to a medical prescription should be approved primarily for short term treatment, e.g. when the possibility of "masking" could occur.

(b) An indirect danger is also present if wider use of a medicinal product would increase the risk of resistance to the product, in particular in the general population, to such an extent that the usefulness of any medicinal product is likely to be compromised; or if the symptom is commonly the outward manifestation of a diverse range of underlying pathologies and where the patient cannot easily discern the underlying disease.

1.3 Self-assessment

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[2] Type A: Those that result from exaggeration of a drug's expected pharmacological actions when given in the usual therapeutic dose; normally dose-dependent.

[3] Type B: Those that represent a novel response not expected from known pharmacological action.

(a) It is important that the condition or symptoms, for which a medicinal product not subject to a medical prescription is indicated, can be correctly assessed by the patient and that the product can be used without medical supervision. This means that the patient should be capable of excluding conditions which could appear to be similar to the indications but unsuitable for treatment with the medicine in question.

Account may be taken of the availability of appropriate information sources that would assist the patient in achieving this, including written information or the advice of pharmacist and other health care professionals

(b) The natural course of the disease, the condition, the duration of symptoms and their reoccurrence and consequences due to this should be correctly self-assessable.

(c) Contraindications, interactions, warnings and precautions should be those which can be understood by the consumer.

1.4 Risk and consequences of incorrect use

(a) A high incidence of conditions listed as contraindications, precautions or warnings, or a high rate of usage of interacting drugs in the population, in case of patients likely to use the medicine, may increase the incidence and risk of misuse; (see below, 1.5 *Patient information*)

(b) It is important that the danger to health is small, if the patient uses the product where it is not indicated, uses it for a longer period than recommended, exceeds the recommended dose or fail to heed warnings or contraindications. Consideration of the consequences of misuse is an important component of the overall safety profile of the medicinal product which should be reflected in the label (as provided for in Article 2.1 g)and n) of Council Directive 92/27/EEC) and/or the leaflet.

1.5 Patient information

(a) The way in which a medicinal product not subject to medical prescription is used is likely to differ from the way the same product was used when available only on prescription, even when the indications are the same or in the same therapeutic area. There is also the risk that the patient will consider the medicinal product not subject to a medical prescription as being less dangerous than when the same product is subject to a medical prescription. This should be taken into consideration.

(b) The written information (leaflet and label) must contribute effectively to safe and effective use of the medicine. The correct use of the medicine should be explained in the information. It is necessary to consider if the information is clear enough for the patients to use the medicine appropriately. This information should be sufficient so that it substitutes for the absence of medical supervision.

(c) The written information supplied with the medicine, in addition to the supervision of the pharmacist when applicable, should be adequate to guard against a risk of using the product where it is contraindicated or unsafe. Contraindications, interactions, warnings and precautions need to be clearly described in layman's terms and prominently presented in the leaflet. See also the guideline on the readability of the label and package leaflet).

(d) In order to minimise risk and maximise benefit, the leaflet and the label should describe the situations where the product should not be used, in at least as much detail and prominence as to when it may be used (see above, 1.4 Risk and consequences of incorrect use) and in accordance with the SPC.

The patient is likely to need guidance on action to take if the medicine does not have the desired effect or cause an adverse effect. The product information (leaflet and label) should in such cases recommend appropriate action e.g. consulting a doctor or a pharmacist within the time stated in the label/leaflet.

2. Second Criterion

Medicinal products shall be subject to medical prescription when they are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health.

In considering whether this criterion applies, the following factor should be addressed.

2.1 Known incorrect use

Known incorrect use for products not subject to a medical prescription (e.g. used for the purpose of increasing the effects of alcohol), could lead to restrictions on the product or reclassification for supply subject to a medical prescription (see also **6. Other Considerations** on page 7). Under such circumstances, classifying the medicinal product as not subject to a medical prescription should not be considered.

3. Third Criterion

Medicinal products shall be subject to medical prescription when they contain substances or preparations thereof the activity and/or side-effects of which require further investigation.

In considering whether this criterion applies, the following factors should be addressed.

3.1 Recent authorisation/limited experience

(a) Further investigation may be necessary when a medicinal product has only recently been granted a marketing authorisation or because of limited experience/use of the product e.g. low sales. Experience in other EU Member States and in other markets, which have sufficient post marketing surveillance, should be taken into consideration.

(b) Even if clinical trial data are extensive and reassuring, it is important to have post-marketing experience in the general population, that is evidence of safety when the product is being used without the exclusion of certain groups of patients, which may be imposed by the design of clinical trials e.g. the elderly, children, certain racial or phenotypic groups and those having certain medical conditions. Products which have different safety or efficacy profiles in different racial or phenotypic groups may need special warnings.

3.2 New strength, dose, route of administration, indication, new age group or combination of substances.

(a) Further investigation is likely to be necessary when it is proposed that the medicinal product will be available without prescription in a new strength, at a new dose, using a new route of administration, new age group or for a new indication particularly when the indication has not previously been authorised for a medicinal product not subject to a medical prescription. A lower dose or a lower strength does not necessarily render further investigation necessary, but it is necessary to confirm that the reduced dose retains the efficacy.

(b) Even though the safety profile of the medicinal product while it was subject to a medical prescription is relevant, a re-evaluation of the risk to benefit ratio is necessary. However, this may be difficult because the product will not have been widely available for the new indication or new dosage. It may, nevertheless, be possible to extrapolate from the safety of the existing prescription product. This is particularly true if there are few side-effects and/or when doses proposed for supply without a prescription are lower and the population is a sub-group of the patient group treated while the medicinal product was subject to medical prescription.

(c) A medicinal product containing a combination of two active substances, which are available in two separate medicinal products, both of which are not subject to a medical prescription, would not automatically be classified for supply not subject to a medical prescription, but would be evaluated in line with the 'Guideline on Fixed-combination products' (Rules governing medicinal products Volume 3C).

4. Fourth Criterion

Medicinal products shall be subject to medical prescription when they are normally prescribed by a doctor to be administered parenterally(for injection).

In considering whether this criterion applies, the following factor should be addressed.

- Parenteral products should normally be subject to a medical prescription, because of the additional risks and complexity of the route of administration.

5. The criteria in Article 3.2 ('special Rx') and Article 3.3 ('restricted Rx') of Council Directive 92/26/EEC

Classification of a medicinal product as not subject to a medical prescription should not be considered whenever these criteria apply, subject to Article 3.4 – see next paragraph.

6. Other Considerations

According to Article 3§4 of Council Directive 92/26/EEC a medicinal product, which meets any of the criteria for supply subject to medical prescription, may be classified for supply not subject to medical prescription if:- the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging and/or other circumstances of use, can make supply without medical prescription appropriate.

6.1 Pack size and package form (container)

(a) The pack size should be decided in relation to the intended length of the treatment. Restricting the availability of a medicinal product to a small pack size is a possible safeguard against misuse, particularly overdose, or a delay in seeking medical attention.

(b) Medicinal products should have a container which as far as possible prevents children gaining access to the medicine, if they get hold of the container.

6.2 Maximum dose, maximum daily dose

Restricting the maximum dose or maximum daily dose may protect against potential danger whether the medicine is used correctly or incorrectly. However it is necessary to confirm that the reduced dose retains the efficacy.

PART 2

The data requirements

The documentation concerning safety and efficacy in support of an application for a change in the classification for the supply will depend on the nature of the active substance and the extent of any changes to the MA. In order to facilitate the evaluation of safety in relation to benefit it should be presented in a logical and concise manner.

1.1 Expert Report

In all cases, an expert report should be provided. The expert should provide a critical analysis of the proposed availability of the product without a medical prescription with the dose and indications as stated in the application. The expert is expected to take a clear position, defend the proposal in light of current scientific knowledge and demonstrate why none of the criteria that determine classification for supply subject to a medical prescription apply to the product.

Advice on the format of expert reports can be found in Volume IIB of the *Notice to Applicants for Marketing Authorisations for Medicinal Products for Human Use in the Member States of the European Community.*

All of the points in Part 1 of this guideline should be addressed and supporting documentation submitted, when applicable. Some of these points are commented on below.

1.2 Safety

(a) A summary of, or references to, animal studies or studies on humans that show low general toxicity and no relevant reproductive toxicity, genotoxic or carcinogenic properties relevant to the experience/exposure of the product should be given.

(b) Experience in terms of patient exposure to the substance needs to be considerable and should be outlined. Normally, active substances which are suitable for supply without a medical prescription will have been in widespread use for five years, in medicinal products subject to a medical prescription. However, provided enough data is available, this does not exclude the possibility of an authority accepting a shorter time; for instance, if the active substance has been in use , other than in a medicinal product (e.g. in a foodstuff or as a metabolite of a known active substance). Adverse drug reactions to the pharmaceutical form and dose proposed for supply not subject to a medical prescription should in normal conditions be minor and should cease on discontinuing therapy.

(c) Information on adverse reactions should be provided, including experience of use without medical supervision, for example in another Member State or in a third country. Variables such as numbers of patients treated, demographic details, indications for use and dose should be provided and taken into account in providing and interpreting the data.

(d) The safety profile should be summarised according to EU guidelines, including reports of and data from postmarketing surveillance studies, clinical trials and published literature presenting the issue of drug safety. Information concerning serious type A and type B reactions should be given and discussed. The problems of extrapolating data from the population, using the active substance supplied only on a medical prescription, to the population using it without a medical prescription should be presented and discussed.

(e) The application should consider the potential for and consequences of drug interactions, in

particular with commonly prescribed drugs.

(f) The application should consider the consequences concerning misuse, e.g. use for longer periods than recommended, as well as accidental or intended overdose and the use of higher doses, should be discussed.

(g) The application should consider the consequences of the use of the product by a patient who has incorrectly assessed his condition or symptoms.

(h) The application should consider the consequences of incorrect or delayed diagnosis of a patient's condition or symptoms due to self medication with the product.

1.3 Efficacy

(a) Evidence of the product's efficacy is not normally considered in the application for changing the classification for supply, unless this application also includes changes to the indications or posology.

(b) If other parts of the dossier are changed, e.g. indication, posology or strength, then supporting data should be provided.

(c) A suitable time-period for treatment of the suggested indication(s) should be justified and given together with a proposed pack size.

1.4 Product information

(a) For a medicinal product classified for supply without a medical prescription, the proposed product label and leaflet are important elements of the application and will be closely examined for comprehensive information and effectiveness in protecting patients from any safety hazards.

(b) Leaflets should provide information on/appropriately describe the use of the product and the circumstances when referral for medical advice is appropriate.

(c) Labels should provide instructions on the use of products for self medication, as required by Article 2.1 n) of Council directive 92/27/EEC.

(d) Contraindications and warnings, such as advice limiting duration of treatment or the need to consult a doctor in certain situations, should be provided as appropriate.

(e) This product information, on the label and in the leaflet, should be readable, see the *guideline on the readability of the label and package leaflet*

1.5 Other

A change of container should be discussed when applicable, together with necessary documentation.

Law on Advertising in the Healthing Care System of October 18, 1978 in the version of the notification of October 19, 1994 amended pursuant to the Eighth Law amending the Drug Law of September 7, 1998 (Federal Gazette I, p. 2649)

Article 1

§ 1

(1) This law applies to advertising for
   1. medicinal products as defined in § 2 of the Drug Law
   2. other preparations, procedures, treatment methods and objects insofar as the advertising statements are related to the diagnosis, cure or alleviation of disease, affliction, injury or pathological ailments in humans and animals.

(2) Other preparations within the purview of par. 1 sub-par. 2 are cosmetic products as defined by § 4 of the Law on Foodstuffs and Consumer Goods. Objects within the purview of par. 1 sub-par. 2 are products for body care as defined by § 5 par. 1 sub-par. 4 of the Law on Foodstuffs and Consumer Goods.

(3) For the purposes of this law, advertising is also the announcement or offering of advertising statements to which this law applies.

(4) This law does not apply to advertising of products for the prevention of accidental damages.

§ 2

For the purposes of this law, the term 'health professionals' is defined as the members of healthcare professions and healthcare occupations, organizations that serve human or animal health, and other persons insofar as they are involved in the legal trade of medicinal products, procedures, treatment methods, objects or other preparations or use such products in the course of their professional activity.

§ 3

Misleading advertising is inadmissible. Advertising is misleading especially

1. when medicinal products, procedures, treatments, objects or other preparations are attributed with therapeutic efficacy or effects that they don't possess;

2. when it gives the false impression that
   a) success is guaranteed,
   b) the recommended or long-term use has no side effects,
   c) the advertisement does not serve competitive purposes;
3. when it contains improper or misleading information
   a) concerning the composition or properties of medicinal products, objects or other preparations or the manner of a procedure or treatment;
   b) or concerning the character, education, qualifications or success of the manufacturer, inventor or persons in their employ.

§ 3a

Advertising for medicinal products that require a marketing authorization and have not been authorized pursuant to the laws governing medicinal products or is not considered as having a marketing authorization is inadmissible.

§ 4

(1) All advertising for medicinal products as defined by § 2 par. 1 or par. 2 sub-par. 1 of the Drug Law must contain the following particulars:
1. the name or company and permanent address of the pharmaceutical undertaking;
2. the name of the medicinal product;
3. the composition of the medicinal product pursuant to § 11 par. 1 sentence 1 sub-par. 2 of the Drug Law;
4. the therapeutic indication;
5. contra-indications;
6. side effects;
7. special precautions for use insofar as these are required for the labeling of containers and outer packages;
7a. for medicinal products that can be dispensed only on doctor's, dentist's or veterinarian's prescription, the marking 'verschreibungspflichtig' ('prescription only');
8. the waiting period for medicinal products intended for application to animals that are used in the production of foodstuffs;

(1a) When a medicinal product contains only one active constituent, the particulars required by par. 1 sub-par. 2 must be followed by the name of this constituent and include the marking 'Wirkstoff': ('active ingredient':); this does not apply if the name of the active ingredient is contained in the particulars required by par. 1 sub-par. 2.

(2) If the particulars required by par. 1 sub-par. 7, 9 and 13 can not be made, they may be omitted.

(3) Where advertising is directed at persons other than health professionals, the following text must be set apart and clearly distinguished from the other promotional information "For information on risks and side effects please read the package leaflet and consult your doctor or pharmacist" (Zu Risiken und Nebenwirkungen lesen Sie die Packungsbeilage und fragen Sie Ihren Arzt oder Apotheker). In advertisements for medicinal waters the particular 'package leaflet' is to be replaced by 'label' and in advertisements for veterinary medicines the particular 'your doctor' is to be replace by 'veterinarian'. The particulars listed under par. 1 sub-par. 1, 3, 5 and 6 can be omitted. Sentence 1 does not apply to medicinal products that can be sold outside of pharmacies exept when risks or side effects are indicated in the package leaflet or on the container.

(4) The particulars required by par. 1 must be set apart and clearly distinguished from the other promotional information and be clearly legible.

(5) Advertisement in audiovisual media must be be succeeded by the text according to par. 3, which must be broadcasted in television against a neutral background in legible characters and at the same time spoken aloud, in so far as this text cannot be omitted according to par. 3 sentence 4. The particulars listed under par. 1 can be omitted.

(6) Pars. 1, 1a, 3, and 5 do not apply if the advertisement is indented as a reminder. Reminder advertising is given when an advertisement contains only the name of a medicinal product or in addition to the name of the medicinal product, the name, company or trademark* of the pharmaceutical undertaking or the marking: "Wirkstoff:" ('active ingredient:').

§ 4a

It is inadmissible to advertise for other medicinal products or preparations on the package leaflet of a medicinal product.

§ 5

Advertising for homeopathic medicinal products that are registered in accordance with the Drug Law or have been exempted from registration can not mention therapeutic indications.

§ 6

Advertising is inadmissible if
1. expertises or recommendations are published or mentioned that were authored by persons without scientific or professional qualifications and

*) Amended by Art. 3 of the Trademark Reform Act of October 25, 1994 (Federal Gazette I, p. 3145)

don't contain the name, profession and address of the expert or issuer of the recommendation and the date of issue of the expertise or recommendation;
2. reference is made to scientific, professional or other publications without it being made evident whether the publication refers to the medicinal product, procedure, treatment, object or other preparation for which the advertising is made and without specifying the name of the author, the date of publication and the source;
3. quotations, tables or other illustrative material taken from professional literature are not reproduced literally.

§ 7

(1) It is inadmissible to offer, announce or supply hospitalities or other promotional gifts (products or services) unless they are inexpensive objects that are marked by a permanent and legible inscription with the name of the advertiser and/or the medicinal product, they are inexpensive small gifts, or they are promotional gifts that would be allowed as a present. Without prejudice to sentence 1, promotional gifts to health professionals are only admissible when they are relevant to the practice of human or veterinary medicine or to pharmacy practice. § 47 par. 3 of the Drug Law remains unaffected.
(2) Par. 1 does not apply to hospitalities offered at events for purely professional and scientific purposes as long as these hospitalities remain within reasonable limits and, in particular, remain subordinate to the scientific objective of the event and are not extended to persons other than health professionals.

§ 8

(1) Advertising which has as its direct or indirect objective the mail-order distribution of medicinal products that can only be dispensed by pharmacies is inadmissible. This prohibition does not apply to advertising related to the distribution of medicinal products in the cases of § 47 of the Drug Law.
(2) Advertising for purchase of certain medicinal products by means of single-item importation as defined by § 73 par. 2 sub-par. 6a or § 73 par. 3 of the drug law or by means of teleshopping is inadmissible.

§ 9

Advertising for diagnosis or treatment that is not based on the personal observation of the disease, affliction, injury or pathological ailment in the person or animal that is to be treated is inadmissible ('distant treatment').

§ 10

(1) Medicinal products that are available on medical prescription only can be advertised solely to doctors, dentists, veterinarians, pharmacists and persons with a permit to trade in these medicinal products.
(2) Medicinal products that are intended to alleviate insomnia or psychological disorders or to affect the mood of humans may not be advertised to persons other than health professionals.

§ 11

Advertising for medicinal products, procedures, treatment methods, objects or other preparations to persons other than health professionals may not contain
1. expertises, references, scientific or professional publications or references thereto;
2. statements that the medicinal product, procedure, treatment method, object or other preparation is recommended, tested or used by doctors, dentists, veterinarians or other health professionals;
3. the description of or reference to case histories;
4. pictorial representations of persons in the work clothing or on the process of carrying out the activities of health professionals;
5. pictorial representations
   a) of changes in the human body or parts thereof due to disease, affliction or injury;
   b) of the effects of a medicinal product, procedure, treatment method, object or other preparation by means of comparative representations of a body's condition or appearance before and after treatment;
   c) of the process by which a medicinal product, procedure, treatment method, object or other preparation affects the human body or parts thereof;
6. foreign or professional terminology insofar as these have not become part of the general German vocabulary;
7. statements that tend to instill or exploit fear;
8. promotional speeches that include offers for the supply or acceptance of addresses;
9. publications that are not identified as advertisements in clear and understandable terms;
10. publications that suggest that a certain disease, affliction, injury or pathological ailment in humans can be determined through self-diagnosis and treated with the advertised medicinal products, procedures, treatment methods, objects or other preparations, as well as the corresponding instructions in audiovisual media;

11. statements by third parties, especially expressions of gratitude or acknowledgment or letters of recommendation, or references to such statements;
12. promotional measures that are directed exclusively or primarily at children under 14;
13. contests, raffles or other procedures with results that are determined by chance;
14. the distribution of free samples of medicinal products or of vouchers for medicinal products;
15. the unsolicited distribution of free samples of other products or objects or of vouchers for other products or objects.

§ 12

(1) The advertising of medicinal products to persons other than health professionals shall not mention the diagnosis, prevention, cure or alleviation of the diseases or afflictions in humans or animals that are listed in the annex to this law.

(2) The advertising for other products, procedures, treatment methods or objects to persons other than health professionals shall not mention the diagnosis, cure or alleviation of these diseases or afflictions. This does not apply to advertising for procedures or treatment methods in spas, health resorts and health resort facilities.

§ 13

Advertising by an undertaking with a permanent address that is not within the jurisdiction of this law is inadmissible unless an undertaking with a permanent address or a person with a usual place of residence within the jurisdiction of this law or in another Member State of the European Community or in another country that is party to the Convention on the European Economic Area and who is subject to the full scope of criminal prosecution has been expressly entrusted to assume the obligations that arise from this law.

§ 14

Infringements against the prohibition of misleading advertising (§ 3) are punishable with up to one year of imprisonment or a fine.

§ 15

(1) Illegal actions are given when a person willfully or negligently
1. engages in advertising that does not contain the particulars required by § 4 or, contrary to § 5, contains particulars concerning therapeutic indications;
2. uses expertises, recommendations or references to publications in a way that is contrary to § 6;
3. engages in advertising with hospitalities or other promotional gifts that is contrary to § 7;
4. engages in advertising that is contrary to § 8 par. 1 sentence 1 or par. 2.
5. promotes 'distant treatment' contrary to § 9;
6. promotes the medicinal products listed in § 10;
7. advertises to persons other than health professionals in a way that is prohibited by § 11;
8. engages in advertising that is related to the diseases or afflictions listed in the annex to § 12;
9. engages in advertising that is prohibited by § 13.

(2) Illegal actions are also given when a person negligently violates the prohibition of misleading advertising (§ 3).

(3) A summary offense against par. 1 is punishable by a fine of up to fifty thousand German marks, a summary offense against par. 2 is punishable by a fine of up to twenty-five thousand German marks.

§ 16

Promotional material that is related to a criminal offense according to § 14 or a summary offense according to § 15 can be confiscated.

§ 17

Not affected by this law are:
1. the Law Against Unfair Competition as published in the adjusted version in the Federal Gazette Part III, Section number 43-1, last amended by Article 14 of the Law on March 10, 1975 (Federal Gazette I, p. 685),
2. § 21 of the Law for Combating Venereal Disease as published in the adjusted version in the Federal Gazette Part III, Section number 2126-4, last amended by Article 66 of the law on March 2, 1974 (Federal Gazette I, p. 469).

3. the Ordinance on Free Gifts as published in the adjusted version in the Federal Gazette Part III, Section number 43-4-1, last amended by Article 141 of the law on March 2, 1974 (Federal Gazette I, p. 469).

§ 18

Promotional advertising that does not observe the provisions laid down in § 4, but observes those provisions of this law in the version that was effective up to September 10, 1998, may be used until March 31, 1999.

Article 2 – 4
(void)

Article 5

Par. 1 (effective date)
Par. 2 (void)

Enclosure (to § 12)

Diseases and Afflictions Which Can Not Be Mentioned in Advertising Pursuant to § 12

A. Human diseases and afflictions

1. Diseases which must be registered in accordance with the Law on Communicable Diseases as published in the adjusted version in the Federal Gazette Part III, Section number 2126-1, last amended by Article 4 of the law on August 10, 1978 (Federal Gazette I, p. 1217);
2. Tumoral diseases;
3. Metabolic diseases or diseases of the internal secretion organs except for vitamin and mineral deficiencies and alimentary obesity;
4. Blood diseases and disease of the blood forming organs except for iron deficiency anemia;
5. Organic diseases of
   a) the nervous system,
   b) the eyes and ears,
   c) the heart and vascular system, except for arteriosclerosis, varicose veins and frostbite,
   d) the liver and pancreas,
   e) the urinary tract and sexual organs;
6. Tumors of the stomach and intestines;
7. Epilepsy;
8. Psychiatric disorders;
9. Alcoholism;
10. Pathological complications during pregnancy, child-birth or childbed.

B. Animal disease and afflictions

1. Diseases which must be registered in accordance with the Law on Communicable Diseases in Animals in the version of the notification of February 23, 1977 (Federal Gazette I, p. 313, 437);
2. Contagious vaginal catarrh in cattle;
3. Fertility disorders in horses and cattle;
4. Infectious breeding diseases of animals;
5. Bacterial diseases of the udder in cows, goats and sheep;
6. Cólics in horses and cattle.

HERBAL FORUM

Position Paper

TRADITIONAL HERBAL MEDICINAL PRODUCTS DIRECTIVE

ADVERSE REACTION REPORTING SYSTEM

REPORTING OF ADVERSE REACTIONS

This position paper proposes that the requirements for Complementary and Alternative Medicine (CAM) adverse reaction reporting be applicable to products registered under the Traditional Herbal Medicinal Products Directive (THMPD).

There is a need, not for new or different systems to report herbal interactions/adverse reactions (which would add to the confusion), but for better use of the existing reporting system alongside education of healthcare professionals of the role and validity of Complementary and Alternative Medicine (CAM). The public needs a clear message that they will not be criticised for seeking CAM but encouraged and advised. The safety of herbal medicinal products is of particular importance as the majority of these products are self-prescribed and are used to treat minor and often chronic conditions.

If the public remain intimidated by healthcare professionals, they can also be encouraged to talk directly to manufacturers. The result would be the same, as at present, manufacturers of licensed products are required to pass reports of adverse reactions on to MHRA.

Current adverse reaction reporting systems (via yellow card)

When new drugs come on to the market, there is limited information about their safety profile, which has been obtained from clinical trials. In general, trials involve 2000-3000 patients who take the medicine for a certain length of time, and there are strict conditions for the inclusion of patients in such trials. This means that the patients in whom the medicines are tested may not be fully representative of the patients who will use the medicine when it is marketed. In addition, it is not until large numbers of patients have taken a drug that side-effects that are rare or which appear after long-term use can be detected.

The current UK system for reporting of Adverse Drug Reactions (ADRs) and Interactions applies to all medicinal products and therapeutic substances. The Yellow Card Scheme for reporting spontaneous adverse drug reactions was introduced in 1964. The scheme is administered by the MHRA on behalf of the Committee on Safety of Medicines (CSM). It requires healthcare professionals to complete and return information in a standard format (i.e. a Yellow Card) for collection and analysis. The widely distributed paper versions of the standard yellow forms that are included in the PAGB's OTC Directory, BNF, ABPI Compendium of data sheets and SmPCs, and MIMS can be posted to MHRA (Freepost). Alternatively, an electronic Yellow Card can also be completed on the internet at the MHRA website[1]. There is also a 24 hour free-phone number for healthcare professionals for reporting information on suspected adverse drug reactions[2].

[1] https://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/submityc/ycreporter.htm

[2] 0800 731 6789

Reports of suspected ADRs are submitted to the CSM/MHRA on a voluntary basis by doctors, dentists, pharmacists, nurses, midwives, health visitors, coroners and by pharmaceutical companies under statutory obligations. Doctors are expected to liaise with the manufacturer where necessary to validate reports. Recently, the first phase of facilitated patient reporting of suspected adverse drug reactions via NHS Direct was launched. In general, the Yellow Card Scheme is used to report suspected reactions to licensed medicines only (including **OTC** and **herbal medicines**). However, since October 1996, MHRA have additionally asked doctors, dentists, coroners, pharmacists and nurses to report suspected reactions to **unlicensed herbal remedies**. Adverse incidents associated with medical devices should be also be reported to the MHRA's Medical Device Adverse Incident Centre.

A black triangle is assigned to a product if the drug is an active substance, which has been newly licensed for use in the UK. However, a product containing previously licensed active substances may also be monitored if it meets one or more of the following criteria:

- a new combination of active substances;
- administration via a novel route or drug delivery system;
- a significant new indication which may alter the established benefit-risk profile of that drug.

For new medicines the CSM/MHRA request reports for **all** suspected reactions, while for more established medicines only **serious** reactions should be reported. The healthcare professionals are therefore encouraged to report those cases where a suspicion arises that there is a causal relationship between the medicinal product taken and the suspected reaction experienced. The CSM/MHRA would like to receive all suspected ADRs associated with these "black triangle" products in order to confirm the benefit-risk profile that was established prior to the drug being licensed. The black triangle drugs are intensively monitored for a minimum of two years and the symbol is not generally removed until the safety of the drug is more fully established.

MHRA enters all the Yellow Cards they receive onto their Adverse Drug Reactions On-line Information Tracking (ADROIT) database, which allows them to process and analyse the reports which are then reviewed on a weekly basis in order to identify any potential safety issues. Reports received by the Yellow Card Scheme are in strict confidence. Data are held securely and information revealing the patient's identity is never released without consent.

Like all methods of data collection, the Yellow Card Scheme has its limitations. It is widely accepted that not all adverse reactions are reported. The decision to report a reaction depends on whether or not a healthcare professional suspects that the drug has caused the reaction.

Over-the-counter herbal/complementary products are used for general well-being and to prevent or treat common minor ailments, but they are also used by some people with serious chronic disease. Community pharmacists are specially requested by the MHRA/CSM to focus their reporting on areas such as **OTC products** and **herbal remedies.** Community pharmacists are most likely to interact with consumers of Complementary and Alternative Medicine (CAM) and thus have a role to play in advising on and monitoring the concurrent use of herbal and conventional medicines, and in reporting suspected herbal interactions.[3] For example, the interaction between St John's wort and oral contraceptives is well recognised, but by reporting well-known reactions it may help to further understand the reaction, which in turn may enable clearer advice on how CAM can be used more safely. The herbal interactions do not only involve medicines. There is also a potential for herb-disease interactions where people with certain conditions use herbal remedies. As with all drug interactions, particular attention should be given to the elderly and others with compromised liver and kidney function; those taking several medications; those taking medicines with a narrow therapeutic window or with which serum concentrations are otherwise particularly important e.g. anticoagulants, anticonvulsants etc. Use in children and pregnant and breast-feeding women also need special consideration.

The Yellow Card Scheme collects suspected adverse reaction reports on all herbal remedies, whether or not they are licensed, including herbal remedies made up for individual patients by herbalists. Although some herbal medicines are licensed for use, there are many herbal remedies available from outlets other than pharmacies, or supplied by herbal practitioners which are not licensed. MHRA have requested healthcare professionals to report suspected adverse reactions to any herbal remedy supplemented with the information about the remedy, including its ingredients, source or supplier, if known, and what the product was being used for and if the remedy was supplied by a herbal practitioner, their name and address is also requested. The MHRA also advises the healthcare professionals to retain a sample of the product if the reaction is severe, in case MHRA needs to carry out further investigations.

Extent of under reporting

Under reporting of ADRs is an inevitable feature of any spontaneous reporting scheme. Healthcare professionals tend to apply the Yellow Card Scheme mostly to prescribed products. A potential solution is to increase the pool of reporters (i.e. CAM practitioners). Recent research highlights the fact that people are reluctant to tell their doctors that they are taking herbal products and thus it is probable that adverse reactions to herbal products are under reported[4]. However, in order to fully evaluate the usefulness of the Yellow Card Scheme for reporting of herbal interactions, a survey by MHRA of the usage of the Yellow Card system for herbals is needed. If usage is low, then the question needs to be asked, "Why?"

[3] http://www.pharmj.com/pdf/cpd/pj_20030125_herbal10.pdf

[4] Barnes J et al. Different standards for reporting ADRs to herbal remedies and conventional OTC medicines: face-to-face interviews with 515 users of herbal remedies. *Br J Clin Pharmacol* 1998; **45**: 496-500.

It has been previously suggested that a new scheme specifically for herbal products needs to be created but if, as we suspect, reporting under the current scheme is low, then creating a new scheme will not solve the problem. The current reporting systems of direct healthcare professional reporting to MHRA and Company reporting should remain the mainstay of the system. A dual system would lead to confusion.

A survey of the public on usage and the role of herbal and other complementary therapy found that the public are significantly less likely to report ADRs to healthcare professionals when these occur following the use of a herbal remedy[4].

This suggests that there is a need to change the ideology of public and healthcare professionals to herbal remedies. One clear result of the recent House of Lords report on Complementary and Alternative Medicine (CAM) is that this type of holistic approach to healthcare is popular with the public. One study reported that 40% of GP partnerships in England provide access to CAM for NHS patients although the evidence is that this provision is patchy. "Access to CAM is dependent on the attitude of their particular PCG or Primary Care Trust" (Chapter 9 of the report[5]).

It seems safe to conclude, albeit with caution, that people are wary of mentioning herbal medicine usage to their doctor, in case they get branded as "alternative" and advised to stop using these alternative healthcare products.

Proposals

To bring effect to changes needs, at the very least, consideration of the following points:

To encourage reporting:

- MHRA/CSM articles in "Current Problems on Pharmacovigilance" concerning reporting on herbals and other Complementary and Alternative Medicine (CAM). This needs to be emphasised for herbal remedies including Western, Ayurvedic or Traditional Chinese Medicines (TCM), and OTC medicines and a reminder that reports are wanted.

- Statements on labels/packaging reminding customers to report, either to a healthcare professional or to the manufacturer, anything untoward that occurs as a result of using the herbal remedy.

- Greater encouragement by MHRA on industry and healthcare professionals to liaise to establish the validity of reports.

- Extended role of CAM practitioners to report adverse reactions to THMPD products

- Clarification by MHRA to herbal suppliers of the law requiring companies to report adverse events, which come to the notice of the manufacturer.

[5] http://www.parliament.the-stationery-office.co.uk/pa/ld199900/ldselect/ldsctech/123/12320.htm

Manufacturers' role

European law requires companies to report adverse events to the MHRA when they receive complaints or reports from members of the public or healthcare professionals. Manufacturers of products registered under the proposed Directive would be required to comply with the provisions on pharmacovigilance set out in Articles 101—108 of Directive 2001/83/EC

Manufacturers should:

- Have access to an appropriately Qualified Person (QP) responsible for pharmacovigilance at all times - (*see Article 103 Directive 2001/83/EC*)

- Have in place an adequate pharmacovigilance system to maintain detailed records of all suspected ADRs occurring world-wide - (*see Article 104 Directive 2001/83/EC*)

- Report all serious suspected ADRs within 15 calendar days to the Licensing Authority (including those ADRS occurring in third countries) - (*see Articles 104 and 105 Directive 2001/83/EC*)

- Include all other suspected ADRs as part of periodic safety update reports (PSURs) (*see Article 104 (6) Directive 2001/83/EC*). (PSURs also include a scientific evaluation of the benefits and risks of the product)

Only manufacturers of licensed herbal products are required to record and submit data on safety aspects to the MHRA.

Manufacturers of unlicensed herbal products currently have no such obligation. However, the Herbal Forum encourages manufacturers of both licensed and unlicensed products to follow the Standard Operating Procedure **(*see Annex 1*)** on reporting of adverse reactions, and for the future proposes that it becomes mandatory for manufacturers or marketers of products registered under the Traditional Herbal Medicinal Products Directive to use this system

Medium to Long-term vision

To increase appreciation and awareness amongst healthcare professionals of the validity of Complementary and Alternative Medicine

- Herbal modular courses available in undergraduate, postgraduate and continuing education courses. (HF acknowledges that reminders are placed in the "CSM Current Problems on Pharmacovigilance")

- Peer reviewed articles and papers in respected journals

- Active support by professional bodies. (HF would welcome representation at RSPGB's Scientific Committee meeting when discussing Phytotherapy issues)

- Information on available widely used herbal remedies and their uses/interactions to be made available to healthcare professionals in publications such as the British National Formulary (BNF) and MIMS. (HF notes that the BNF has included interactions of St John's wort)

Herbal Forum
June 2003
S Shah
30/6/03

Relevant Weblinks

- MHRA online information service to give up-to-date advice on herbal medicines safety:
  http://medicines.mhra.gov.uk/whatsnew/pressreleases/herbalsafety.htm

- MHRA Report on Safety of Herbal Medicinal Products:
  http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbalmeds/HerbalsSafetyReportJuly2002_Final.pdf

- Guidance notes are available to provide an understanding of why and how suspected adverse drug reactions should be reported:
  http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/ycguidancenotes.pdf

- Monitoring the safety and quality of medicines - The Yellow Card Scheme:
  http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/yellowcardscheme.htm

- Complementary and alternative medicine, House of Lords Select Committee on Science and Technology, 6th report 1999-2000 [HL123], The Stationery Office, London (£15.50).
  http://www.parliament.the-stationery-office.co.uk/pa/ld199900/ldselect/ldsctech/123/12301.htm

Annex 1

Standard Operating Procedure for Adverse Reaction Reporting Procedure for products registered under Traditional Herbal Medicinal Products Directive (THMPD).

Purpose:
To ensure the efficient handling of all adverse reactions reported to the Company.

Scope:
All products marketed by the Company and its affiliates.

Responsibility:
The Qualified Person residing in the European Community is the person responsible for establishment and maintenance of a Pharmacovigilance system and for ensuring compliance with this procedure. The QP will be responsible for appropriate deputising arrangements in his/her absence.

Definitions:

Serious Adverse Reactions
Serious reactions include those that are fatal, life-threatening, disabling, incapacitating or which result in or prolong hospitalisation and/or are medically significant. Other reactions that are considered serious include congenital abnormalities. {PRIVATE "TYPE=PICT;ALT=PDF icon"}Examples of some reactions that are considered which are medically significant are available at: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/whatisserious.pdf

Adverse Reaction
An adverse reaction is an unwanted or harmful reaction experienced following the administration of a THMPD registered product or combination of products and is suspected to be related to the treatment. The reaction may be a known side-effect of the drug or it may be a new previously unrecognised adverse reaction.

Side-effects
Adverse reactions expected with proper and correct use of the product, details of which are included on the product labelling.

Procedures:

(i) Adverse reactions may be reported to the Company by various routes and by various persons (e.g. consumers, health professionals, company representatives). In any event, **all** reports of adverse reactions should be reported to the QP through

a specified company procedure. Marketing authorisation holder (MAH) shall use internationally agreed medical terminology for the reporting of adverse reactions.

ii) The Company QP shall review such reports and after consultation with the Drug Safety Officer and/or Medical Adviser (where appropriate) shall determine the type of adverse reaction. For further explanation of types of Adverse drug reactions (ADR), refer to MHRA Guidance Notes on Suspected ADR reporting at: http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/yellowcard/ycguidance notes.pdf

iii) The minimum information includes the following details:

- Name of the suspected THMPD registered product
- Route and dates of administration
- Daily dose
- Strength, batch details, and expiry date of THMPD registered product
- Indication for which the THMPD registered product was used
- Description of suspect reaction including a diagnosis if relevant
- Record of whether the adverse reaction was serious, and if so, the reasons why
- Outcome of the adverse reaction
- Initials and a local identification number of person affected (e.g. the GP/Hospital reference number)
- Age of person at the time adverse reaction occurred
- Gender
- An identifiable source, wherever possible this should include the name of the reporter and his/her designation and the Company address
- If possible, indicate whether or not the person affected was on any other medication or THMPD registered product in the last 3 months.
- Include any suspected interactions (e.g. THMPD registered product—disease interaction; THMPD registered product—medicine interaction)

iv) Serious Adverse Reactions

(a) *Licensed and THMPD Registered Products*
The QP shall complete the appropriate form as fully as possible and forward it to the Competent Authority. Serious adverse reactions reported to the Competent Authority **MUST** be substantiated by a medically qualified doctor, dentist, pharmacist, coroner, nurse or herbal practitioner. Such a report should be made immediately and in all cases within 15 days of receipt of the report.

Any actions or alterations to the Licence requested by the Competent Authority or by the Company shall be actioned within a reasonable time frame.

(b) *Unlicensed Products*
The QP should complete the report as fully as possible, but clearly indicating the product is a "FOOD" or "COSMETIC" and send to the Competent Authority immediately.

(c) *Third Company Owned Products*
Where a serious adverse reaction is reported on a third company owned product, a report should be completed as fully as possible and forwarded to the third company immediately.

(v) Adverse Reactions:
If the report is deemed to be a minor adverse reaction to a product registered under THMPD, the Competent Authority still needs to be informed by the accepted Suitably Qualified person. The MHRA have specifically requested that **all** suspected ADRs/interactions be reported for herbal remedies.

(vi) Periodic Safety Update Reports
For licensed products (in line with Directive 2001/83/EC), and those products registered under THMPD, a Periodic Safety Update Reports (PSUR) should be generated by the QP either immediately upon request or periodically as follows:

- Every 6 months for the first 2 years after authorisation
- Every year for the following 2 years
- Thereafter at 3-yearly intervals[s1]

A copy of the report is sent to all appropriate Competent Authorities (i.e. where the product is registered as a medicine and marketed)

(ix) Records

Copies of Complaints – held for appropriate period defined by the Company

Periodic Safety Update Reports (PSURs) – held for the life of the product.

Page: 11
[s1]Source 12/6/03 Amended proposal. Is this necessary for herbal products the Directive gives 2 options – should manufacturers wait until asked by MHRA or do it periodically?

GERMANY

Area:	357 020.8 km²
Inhabitants (2001):	82 371 000
Population density (2001):	230.7 inhabitants per km²
Gross Domestic Product (2001):	DEM 4 036.25 billion = € 2 064.4 billion
Healthcare expenditure (*Gesetzliche Krankenversicherung*) (2001):	DEM 265.1 billion = € 135.54 billion
Healthcare expenditure as a % of GDP 2001:	6.57%

1. CLASSIFICATION

The criteria for the classification of medicinal products have been the same nation-wide since 1961. As these criteria were fully in line with the EU's classification provisions (laid down in Title VI of the *Community code*), no further measures were necessary to implement this Directive into the German Medicines Law (*Arzneimittelgesetz* or AMG).

There are two medicine classes in Germany: prescription-only and non-prescription. Classification as prescription-only depends on the substance(s). By statutory regulation, this classification may be limited to particular dosages, strengths, presentation forms or applications. Some non-prescription medicines are released for sale outside pharmacy (for conditions see point 7).

Herbal medicinal products are medicines containing as active ingredients only plants, parts of plants or plant materials, or combinations thereof, whether in crude or processed state. Most herbal medicinal products are available for self-medication without a medical prescription.

For homeopathic medicines, there has been a simplified registration procedure (no proof of efficacy) since 1978. Therefore, only the provisions on the mutual recognition of simplified registrations in Directive 92/73/EEC on homeopathic medicines had to be implemented by the 5th Amendment to the Medicines Law (*Arzneimittelgesetz* or AMG). This was published in the *Bundesgesetzblatt* of 16.8.1994 and entered into force on 17.8.1994.

As for vitamins and minerals, German legislation defines on the one hand which products are medicines or are considered as such. On the other hand, it makes clear that specific products, e.g. foodstuffs according to § 1 of the German Food Law (*Lebensmittel- und Bedarfsgegenstände-Gesetz* or LMBG), are generally not considered as medicines. The main criterion for the legal differentiation between medicines and foodstuffs is the objective determination of the product's predominant purpose according to the common opinion/interpretation of the trade. Criteria that may be used include composition, posology and claims. Additional less important criteria might include dosage form (particularly for vitamins and minerals), labelling, retail outlet or price.

Until the mid 1980s, the Federal Health Authorities (formerly BGA) granted marketing authorisations for multivitamins with the main indication "prevention and treatment of vitamin deficiency." In some cases, the dosage was entirely within the range that is also

acceptable for foodstuffs. Apart from the fact that vitamins A, D and some forms of vitamin K are prohibited in foodstuffs for general consumption, there is no legal definition of upper dosage limits for vitamins. On the other hand, dosage is one of the criteria determining the objective purpose of a product. Therefore an Expert Working Group within the Federal Food Inspection authorities in official practice uses an upper dosage limit of three times (vitamins) and about the one time (minerals) the German RDA as fixed by the *Deutsche Gesellschaft für Ernährung*. Beyond medicinal products, there is no category of "health products" in Germany.

On 5.12.1997, the Federal Ministry of Foodstuffs, Agriculture and Economy announced that, according to § 47 a of the Food Law (LMBG), food supplements containing certain trace elements in tablet form which had been lawfully placed on the market in any Member State of the European Union or of the European Economic Area (EEA), could be sold in Germany provided they did not contain more than the following recommended daily allowances (RDAs): Iron, 5 mg; Zinc, 5 mg; Copper, 1 mg; Chromium, 60 µg; Selenium, 30 µg; Molybdene, 80 µg.

In mid 1999, the European Commission sent a reasoned opinion (the second stage of infringement proceedings under Article 226 of the EC Treaty) to Germany because of the country's excessive delays in issuing import authorisations for food supplements. In Germany, food legally produced and/or marketed in another Member State which does not correspond to the provisions of German food law are subject to an authorisation procedure. This procedure is used by the German authorities to check that there is no danger to public health and lasts on average from six to nine months in the case of food supplements. The Commission considered that the length of this procedure constitutes an unjustified barrier to entering the German market. The German Government argued on the other hand that the delays are the result of the complexity of the process to decide whether a food supplement should be classified as a foodstuff or as a medicine, the workload of the competent authorities and the extremely high number of requests. The Commission stated in its reasoned opinion that delays for processing requests for authorisation for food supplements well in excess of 90 days constitute an infringement of EC Treaty rules on the free movement of goods.

After receiving a number of complaints, the European Commission decided in mid 1999 to refer Germany to the European Court of Justice (ECJ) for erecting unjustified barriers to the sale of vitamin-enriched food supplements imported from other Member States (in breach of Article 28 (ex 30) of the EC Treaty). On account of the levels of vitamins in these products, the German authorities classify some of these as medicinal products. The effect of this classification is that they are subject to a long and costly authorisation procedure. The Commission had pointed out to Germany that the systematic application of a purely quantitative criterion (three times the recommended daily intake) does not take account of the differences between the various types of vitamins and the different levels of risk involved in the event of excessive consumption. A less restrictive measure would, according to the Commission, be to specify a limit value for each vitamin above which a preparation would be regarded as a medicinal product. The German authorities have so far refused to change their legislation.

2. REGISTRATION

Non-prescription medicines are registered in Germany in accordance with EC rules. According to industry experience, the average time to obtain a licence is 2-3 years for chemical substances and 12-18 months for herbal medicinal products.

Germany has a major problem with the implementation of EU legislation in that the marketing authorisations of all old medicines had to be reviewed before 20.5.1990. The broad range of medicines marketed in Germany and the sophisticated review procedure was causing considerable delay in these reviews, meaning that the deadline could not be kept.

As the backlog was likely to take a considerable number of years to clear, the German Health Minister in 1994 proposed an action plan to speed up the review process. The changes (laid down in the 5th Amendment of the German Medicines Law enacted in August 1994) limited the pharmaceutical industry's possibilities to bring changes to a registered medicine, to oppose registration decisions and to deliver *Rücknahme-erklärungen* allowing the medicines concerned to stay on the market until the end of 2004.

Given that the review process was still not completed and under pressure from the European Commission, the German government in October 1999 proposed a 10th amendment of the German Medicines Law to expedite the authorisation procedures and review process. It entered into force in July 2000. In particular, the period in which the questionnaire must be answered has been shortened from 18 months to 12 months maxiumum. Moreover, all dossiers and documents should be forwarded for all products. Medicinal products not yet reviewed should be labelled as "provisionally licensed." Products which were allowed to stay on the market without being in the re-registration process until the year 2004 (see above) should either return to the re-registration procedure or withdraw.

Under the 7th AMG Amendment enacted on 4.3.1998, a total of 24 Articles of the German Medicines Law were modified to implement a number of pieces of EU legislation, in particular concerning the EU's marketing authorisation system, penalties for non-implementation of EU law and the impact of medicinal products on the environment, if applicable. With regard to the EU's decentralised procedure, the Amendment made the marketing authorisation decisions of other Member States more binding. Applicants were obliged to submit complete information on decisions by the competent national authorities of other Member States concerning applications, licences and refusals, including data on incomplete or interrupted toxicological or analytical tests or clinical trials. The 7th Amendment also addressed the implementation of additional grounds for withdrawal, recall or modification following a binding Commission decision under the decentralised procedure's arbitration procedure (the so-called 'negative rebound effect').

A Notice dated August 1994 on the re-registration of "traditionally used" (herbal) medicinal products was published as §109a of the 5th Amendment to the Medicines Law (*Arzneimittelgesetz* or AMG). An important change was that the health authorities declared they would henceforth accept data on "traditional use" of the active ingredient and no longer require these data for specifically named products. Several hundred "traditionally used" products have thus obtained re-registration.

In the period between 1995 and 2000, the Federal Institute for Drugs and Medical Devices (BfArM) regularly published lists of substances and combinations allowed as traditional medicines. They include around 1 000 substances or combinations of substances which - in defined indications - meet the requirements of "traditionally used" medicinal products. The 8th AMG Amendment (enacted in September 1998) included a provision that the registration criteria for traditional medicines introduced in August 1994 could be used upon the five-yearly marketing authorisation renewal for these substances and combinations.

3. PATIENT INFORMATION

The EU's patient information provisions (Title V of the *Community code*) were implemented in Germany by the 5th Amendment to the Medicines Law (AMG) published in the *Bundesgesetzblatt* of 16.8.1994.

Patient information leaflets are compulsory for newly registered products. So-called old medicines should have a leaflet within one year of re-registration. However, in practice all old medicines are already marketed with leaflets and correct labelling. If a medicinal product is marketed without outer packaging, the leaflet may be omitted provided the basic particulars are displayed on the label.

On 17.8.1994, the German health authorities (BfArM) published a *Notice to Applicants* on the establishment of patient leaflets to guide manufacturers through the new provisions of the 5th Amendment to the AMG. In August 2001 BfArM established, in cooperation with BAH, the German non-prescription medicines manufacturers' association, a revised version which was officially published on 25.1.2002. Although the *Notice to Applicants* does not have legal status, BAH is advising its members to follow the recommendations contained therein on the establishment of user-friendly patient leaflets, in particular the use of questions for the various headings.

Guided by the EC's *"Guideline on the Readability of the Label and Package Leaflet of Medicinal Products for Human Use"* and the new *draft Notice*, a working group of industry and authorities, coordinated by the BAH, worked out new standard package inserts for a few dozen very common active ingredients such as acetylsalicylic acid, acetylcysteine, paracetamol and loperamide.

4. ADVERTISING TO THE GENERAL PUBLIC

The EU's provisions on pharmaceutical advertising laid down in Title VIII of the *Community code* were implemented in Germany by the 5th Amendment to the Medicines Law (AMG) published in the *Bundesgesetzblatt* of 16.8.1994 enacted on 17.8.1994. Since the German advertising law in force at the time was already largely in line with the EU's provisions, the 5th Amendment introduced only a few new provisions. They concerned, e.g.,

- an obligation for companies to appoint an "Information Officer" who is to be responsible for compliance of a company's entire advertising and patient information data with the authorised Summaries of Product Characteristics
- an obligation to include as minimum information the common name of the medicinal product if the product contains only one active ingredient.

OTC advertising to the general public is allowed for all non-prescription medicines (including reimbursed medicines) in all media. Certain indications specified in the EU Directive cannot be advertised to the general public.

In Germany, the requirements for the mandatory text to be included in advertising are nearly the same in all media:

> "For risks and undesirable effects, please read the patient information leaflet and ask your doctor or pharmacist."

Print advertising should moreover include the name of the medicinal product, the therapeutic indications and warnings if appropriate.

Advertising requirements are laid down in the Pharmaceutical Advertising Law (HWG), as follows:

- For television and radio advertising: § 4, Article 5, point 1
- For print advertising: §4, Article 3, point 1. Before the 8th Amendment to the AMG took effect on 11 September 1998, there was an additional requirement to include side effects and contraindications in the print media.

Public advertising of non-prescription medicines is controlled by the 1909 *Law on Unfair Competition* (UWG, amended on 22.6.1998), as well as the pharmaceutical advertising law (*Heilmittelwerbegesetz* of 18.10.1978, amended on 7.9.1998). Guideline 97/55 of 16.10.1997, which was to abolish the current prohibition on comparative advertising in Germany, was implemented in Germany by a new paragraph 2 in the *Law on Unfair Competition*. The special prohibition for comparative public advertising laid down in Art. 5b of the Pharmaceutical Advertising Directive 92/28 had been implemented by § 11 Art. 2 of the pharmaceutical advertising law (*Heilmittelwerbegesetz*). Therefore comparative advertising to the general public is not allowed, except for the comparison of prices.

Public advertising is controlled by authorities, competitors and self-regulatory post-event control carried out for example by Integritas – *Verein für lautere Heilmittelwerbung e.V.*, Bonn.

Sanctions for companies breaching the self-regulatory codes include:

1. A simple letter requesting the company to explain its position before a certain deadline.
2. A warning giving a deadline before which the company should pledge to discontinue the offending advertisement
3. Introduction of an injunction before the court (summary procedure)
4. Court proceedings on the substance of the case, leading to condemnation to discontinue the offending advertisement and payment of a fine.

The German pharmaceutical advertising law also contains special rules for advertising to health professionals. These rules are basically in line with the EU advertising Directive.

The German Constitutional Court found in 1996 that the ban on the advertising of parapharmaceutical products imposed by the different Orders of Pharmacists on their members in Germany was unconstitutional. This meant that pharmacists would in future probably be allowed to advertise all products not classified and registered as medicines as well as those medicines available for sale outside pharmacy. This part of the pharmacy business was estimated to represent around 7%.

According to § 18, Article 1, No. 1 of the Food Law (LMBG), products covered by this Law are not allowed to make medicinal claims. There is consequently no category of "health products" in Germany. It is moreover forbidden to make misleading advertising claims (§ 17, Article 1, No. 5a (exaggerated claims) and 5c (foodstuffs being presented as medicines) of the LMBG).

In 2000, around € 444 million were spent on the public advertising of medicinal products, corresponding to 6.2% of total non-prescription sales and 10.6% of self-medication sales. This amount can be broken down into: magazines: € 164 million; television: € 249 million; daily newspapers: € 24 million; radio: € 5.6 million and outdoor: € 1.5 million.

5. USE OF TRADEMARKS (BRAND NAMES)

In August 1991, the German registration authorities adopted and published guidelines and recommendations for the avoidance of misleading designations for medicinal products. These guidelines also contained the basic regulation for the use of trademarks.

The use of the same trademark for medicinal products with a different active ingredient is generally permitted if the greatest care is taken to avoid any risk of confusion among doctors or patients. This can be achieved through the addition of an appropriate prefix or suffix to the brand name. It is therefore allowed to use the same brand name for medicines of the same and of different product groups, as well as for prescription-only and non-prescription medicines. This does not affect the latter's capacity to advertise to the general public.

It is in general also allowed to use the same trademark for medicines and for, e.g., foodstuffs or cosmetics. However, on the last point the authorities are becoming more restrictive.

6. WASTE

The (first German) Ordinance on the Avoidance of Packaging Waste (*Verpackungs-verordnung*) of 12 June 1991 imposed strict rules on manufacturers and distributors for the recovery and recycling of packaging materials. BAH edited a comprehensive publication to guide its members through the maze of measures under the Packaging Ordinance and its practical implementation for pharmaceutical manufacturers.

In August 1998, a revision of the Ordinance came into force. The new provisions clarified some problems which had arisen in day-to-day practice, and harmonised some of the Ordinance's requirements with European Parliament and Council Directive 94/62/EC of 20 December 1994 on packaging and packaging waste, e.g. concerning heavy metal concentration levels in packaging materials. The first amendment to the Ordinance dated 28 August 2000 laid down the conditions for derogation for plastic crates and plastic pallets with regard to heavy metal concentration levels.

In September 2001, the European Commission adopted a positive decision with obligations vis-à-vis a set of contracts concluded by the *Duales System Deutschland AG* (DSD) concerning its system of selective collection and recovery of sales packaging waste. By this decision, which certifies that there are no grounds for action in respect of DSD's statutes and guarantee agreements and which exempts the service agreements, the Commission for the first time defined two fundamental principles of its competition policy for the waste disposal sector.

Firstly, the Commission explained that it can only accept long-term exclusivity provisions in favour of the collectors in the service agreements concluded between DSD and its collectors when the indispensability of such provisions is justified on the basis of convincing economic evidence.

Secondly, the Commission underlined the importance it attaches to free and unimpeded access to the collection infrastructure for competitors of DSD. Together with the "abuse decision" adopted in this case on 20 April 2001 concerning the payment provisions of the

trademark agreement concluded between DSD and the companies covered by the German Packaging Ordinance, this decision lays down the necessary conditions allowing competition in the area of collection and recovery of packaging waste in Germany.

Each company needs to document by 30 April of each calendar year how it is fulfilling its recovery and recycling duties.

There are no nation-wide rules on the management of pharmaceutical waste, i.e. unused medicinal products. However, in practice most unused medicines are returned to the pharmacy, to be picked up by the waste disposal service (*Hausmüllabholung*).

A recycling company – founded by some generic manufacturers – has set up a recycling system for pharmaceutical packaging including unused medicines for incineration. Following the enforcement of the new packaging ordinance, this Remedica system has steadily been increasing its market share.

7. DISTRIBUTION

In principle, all medicines should be sold in pharmacies. However, the German Medicines Law (Section 44) allows the distribution of certain medicines outside pharmacy through other retail outlets provided a qualified member of staff is present in that outlet at all times. This person should have the necessary knowledge of the filling, packaging, labelling storing and marketing of medicinal products. Section 44 covers medicines marketed exclusively for purposes other than curing or alleviating illness, injuries, aches or pains. Section 45 of the AMG allows for further exemptions even if the conditions in Section 44 are not met, while Section 46 provides for the sale of products meeting the requirements of Section 44 to be nonetheless restricted to pharmacies.

Based upon these provisions, some German companies in 1998 decided to start selling non-pharmacy-bound medicines in BP gas stations, a move publicly attacked by the German pharmacists. In the meantime, whole discussion has blown over as German consumers do not seem accept gas stations as an appropriate place to buy their medicines.

Self-service of non-pharmacy-bound products is permitted in pharmacies and elsewhere. Self-service of pharmacy-only products is prohibited by the Medicines Law (§52). There are no laws or codes limiting the display of non-prescription medicines in pharmacy. Displays are considered as public advertising and hence subject to pharmaceutical advertising law (see point 4).

Germany has approximately 21 700 pharmacies, or one pharmacy for around 3 800 inhabitants. Certain medicinal products can also be bought in the following outlets: 6 300 drugstores and 11 640 self-service drugstores; 2 459 health shops; and 7 505 other retail outlets (food stores, hypermarkets, etc.). There are 21 wholesalers with 106 warehouses.

In Germany, a pharmacy must be owned by a pharmacist. Multiple pharmacy ownership is not allowed. Pharmacies must have a surface of at least 110 m^2, consisting of a customer area, a storeroom, a night-service area, a lavatory, and storage facility with a temperature below 20°C.

8. DISTANCE SELLING

Distance selling is allowed for those medicinal products available for sale outside pharmacy (see point 7). These products may be distributed by mail order. However, mail order business with non-prescription and prescription medicines is forbidden just the same (§ 43 of the Medicines Law - AMG) as is advertising for it (§ 8, Article 1 Pharmaceutical Advertising Law - HWG).

The teleshopping of non-prescription medicines is regulated by law in Germany. Corresponding to the provisions of Directive 97/36/EC, teleshopping is prohibited for all medicinal products according to § 8, Article 2 Pharmaceutival Advertising Law (HWG).

9. PRICING

Manufacturers can set their own prices for all medicinal products, including non-prescription medicines.

Non-prescription medicines are generally reimbursable. However, the first negative list of 1.4.1983 and the second negative list of 1.7.1991 excluded some indications and some products from reimbursement.

A version of the *"Guidelines on the Prescribing of Medicinal Products by Doctors Participating in the Health-Care Scheme"* (*Arzneimittel-Richtlinien*) agreed on 31.8.1993 provided guidance to medical doctors after the introduction of the 1993 delisting measures. They laid down a number of exceptional cases in which doctors were allowed to continue the prescription of certain products they were otherwise no longer allowed to prescribe. As it became clear in the second half of 1996 that medicine costs threatened to exceed the 1996 budget, emergency prescribing guidelines were issued by the Association of German Sick Fund Doctors at the end of 1996.

A new draft of these Prescribing Guidelines was published by the joint committee of doctors and insurance companies in June 1998, laying down in concrete terms when medicinal products could be prescribed and when not. More than 50 groups of medicinal products to be de-reimbursed were listed in an annex. Following comments from industry and pharmacists, the draft was revised and finally adopted by the committee in January 1999. Pharmaceutical companies took legal action against the draft because they felt their rights were infringed. Based on these actions, a court in Hamburg stopped the draft guidelines on 31 March 1999. Therefore, the new guidelines could not come into force – as planned - on 1 April 1999. It is unclear whether and when the new guidelines will finally be adopted and come into force.

The following measures were adopted and implemented in the third health reform at the end of 1995:

- Medicines under patent registered after 31.12.1996 would be entirely excluded from the reference price system. This measure was designed to provide additional support to the research-based pharmaceutical industry in Germany.
- The obligation for pharmacists to supply parallel imported products was abolished.
- The patient co-payment system based on pack size was modified and payments increased on 1.1.1997 from DEM 3, 5 and 7 to DEM 4, 6 and 8. A further increase to DEM 9, 11 and 13, respectively, was implemented on 1.7.1997. This effectively excluded a large

number of non-prescription bound medicines from reimbursement and resulted in a sales decrease for these product in 1997 of 10%. Self-medication sales on the other hand grew in the same period by 4%.

The first legislative action in the healthcare sector of the red/green government elected in October 1998 came into force on 1.1.1999. The law - designed to prepare the 'big' health reform in 2000 - affected the pharmaceutical industry as follows:

- A DEM 1 billion (€ 511 million) cut to the 1999 medicines budget.
- All reference prices could be decreased, leading to further cost savings of DEM 450 million.
- Patient co-payment based on pack size was decreased from DEM 9, 11 and 13 to DEM 8, 9 and 10, respectively.
- The organisations of general practitioners were entitled to inform all GPs on prices, indications and especially on the prescribing of "useful" medicines. With this information, it was expected that the medicines budget could be better controlled and further cost savings realised.

The 'big' health reform came into force on 1 January 2000. The main feature affecting the pharmaceutical industry was the establishment of a positive list of reimbursable medicinal products. The Federal Health Ministry and the competent Commission released a first draft of the so-called "positive list" of reimbursable medicines, substances or combinations for discussion on 13 July 2001.

According to an IMS study ordered by BAH, one third of the current reimbursable medicinal products with total annual sales of four billion euros would be excluded by the draft. If 75% of the excluded products were to be substituted by listed products, the health insurance companies would incur additional expenditure for medicinal products of 1.8 billion euro, demonstrating that positive lists are financially counterproductive and do not yield any cost-saving effects.

BAH's comments on the draft positive list consisting of 1 221 DIN A4 pages and about 500 DIN A4 files provided medicinal/pharmaceutical reasons why the products earmarked for exclusion from reimbursement should remain reimbursable in the future. As a next step, the competent Commission took into consideration the different comments and decided on the draft in spring 2002, after which the Federal Health Ministry is to prepare a ministerial order. This order will be the basis for the final positive list with brand names, which will be binding on all prescribing doctors. According to current plans, the final positive list will - if at all - not come into force before end 2002.

The so-called "aut-idem substitution" measure, meaning that pharmacists are allowed to substitute a prescribed medicine with another cheaper medicine containing identical active substances, entered into force on 24.2.2002. The measure, which covers all reimbursed non-prescription (and prescription) medicines, will cost the pharmaceutical industry 500 million euros per year. The measure was only supported by the German Organisation of Pharmacists. Industry and doctors were heavily opposed.

For medicines available only in pharmacies, there is a uniform retail price for consumers under the Medicine Price Order (*AMPreisV*). Although the measure was under discussion for a long time, an amendment enacted on 1.7.1998 left the structure of the Medicine Price Order intact in that it did not abolish the uniform retail price for non-prescription medicines. However, hefty reductions were brought to wholesale and pharmacy margins for expensive

products (see point 10 below) in order to relieve the health insurance budgets. Pharmacists will be compensated for lack of income following the price cap by higher fees for, e.g., night services. For medicines legally available in other retail outlets than pharmacy, consumer prices are not fixed. As a result, there is no uniformity in pharmacy prices for these products either.

10. PRICE BUILD-UP

Lower priced products	%	%
Manufacturer's selling or ex-factory price (MSP)	100.0	42.4
Wholesale price (margin = 17.4%[1])	121.0	51.3
Pharmacy price excl. VAT (margin = 40.5%[2])	203.5	86.2
Pharmacy price incl. VAT (16%) = consumer price	236.0	100.0

Higher priced products	%	%
Manufacturer's selling or ex-factory price (MSP)	100.0	59.1
Wholesale price (margin = 10.8%[1])	112.0	66.2
Pharmacy price excl. VAT (margin = 23.2%[2])	146.0	86.2
Pharmacy price incl. VAT (16%) = consumer price	169.3	100.0

The standard VAT rate levied on all medicines is 16%. The mark-ups depend on the ex-factory price. The more expensive a product, the lower the mark-up.

11. MARKET DATA

The market data are based on the following model:

- the **total pharmaceutical market** (excluding hospital sales) at consumer price level
- the **total non-prescription medicines market** representing the sales at consumer price level of all non-prescription medicines (as defined in Germany)
- the **self-medication market** representing the sales at consumer price level of all non-prescription medicines bought spontaneously by the consumer. These figures are included in the figures on the non-prescription medicines market.

In DEM millions at consumer price level	1999	2000	2001
Total pharmaceutical market	53200	54900	59985
Total non-prescription market	13400	14000	14300
Self-medication market	8260	8200	8550

In DEM millions at consumer price level	1999	2000	2001
Total pharmaceutical market	27201	28070	30670
Total non-prescription market	7874	7158	7315
Self-medication market	4193	4193	4269

1 Maximum additional charge.

2 Fixed additional charge.

Percentage change over previous year	1999[3]	2000[3]	2001
. Total pharmaceutical market	+6%	+6%	+2%
. Total non-prescription market	+/-0%	-1%	+2%
. Self-medication market	+5%	+5%	+2%

Percentage of total pharmaceutical market	1999	2000	2001
. Total non-prescription market	28.9%	26%	24%
. Self-medication market	15.4%	15%	14%

Main product groups

In DEM millions at consumer price level	1999	2000	2001
Cough and cold	1596	1669	1694
Analgesics	941	[illegible]	[illegible]
Digestives and intestinal remedies	1002	1075	1093
Skin treatment	586	618	655
Vitamins and minerals	758	771	780
In € millions at consumer price level	**1999**	**2000**	**2001**
Cough and cold	816	853	866
Analgesics	481	475	476
Digestives and intestinal remedies	512	550	559
Skin treatment	300	316	335
Vitamins and minerals	388	394	399

12. RESTRICTIONS CONCERNING IMPORTS

There are no restrictions concerning imports from countries within the European Union. The only requirement is that they must have obtained a marketing authorisation at the national level or through the new EU registration procedures (centralised or decentralised). The same goes for imports from the European Economic Area. In order to import medicinal products from other countries, the importer needs an import licence as well as certain other certificates.

13. SWITCH CLIMATE

The procedure for a change of classification status is clearly defined in the German Medicines Law (AMG). In the last few years, a considerable number of switches has been recommended by the German Expert Committee for the Classification of Medicines and subsequently enacted. Below are the main switches with the effective date:

- On 1.1.1996: indomethacin 1% solution for topical use; octenidine and phenoxy-ethanol products except for use in the mouth. Lindane for use in food-producing animals was switched back to prescription control.

3 1999 percentages of change over 1998 and 2000 percentages over 1999 do not correspond to the reported market figures as: (1) IMS changed its basis for calculating prices of medicines sold outside pharmacies. In previous years, these prices were estimated at a level that was around 30% higher than in 1999 and (2) IMS changed the method to calculate the split between the self-medication and the prescribed non-prescription bound market segments.

- On 1.7.1996: hydrocortisone acetate up to 0.25% in a pack size of 50 g, for all indications for use by adults and children over 6; miconazole for the treatment of vaginal mycosis, in a three-day treatment pack; ibuprofen liquid as an analgesic; lactitol for the indication hepatic encephalopathy: fenticonazole for the topical treatment of mycoses.
- On 1.1.1997: azelastine as nasal treatment for seasonal allergic rhinitis (no limitation on pack size); phenylpropanolamine (DL-norephedrine) was switched back to prescription-only status when used as an anorectic agent, whereas the non-prescription status of the ingredient for use in cough and cold remedies was maintained; L-tryptophan was switched back to prescription-only status when used in depression, whereas the non-prescription status of the ingredient for use in sleep aids and all kinds of infusions was maintained.
- On 1.7.1997: beclomethasone dipropionate as nasal treatment of seasonal allergic rhinitis, with restrictions on pack size and use in children.
- On 1.1.1998: loperamide, an antidiarrhoeal for use in children from six to 12 (was already OTC for persons over 12); Levocabastine, a topical antihistamine against allergic symptoms of nose and eye; amorolfine, a topical treatment against mycosis of nails and skin; croconazole, another topical anti-mycotic. At the same time, terfenadine and astemizole were switched back to prescription status following worldwide safety discussions on possible cardiac side effects.
- On 20.1.1998, the German Expert Committee for the Classification of Medicines rejected the Federal Ministry of Health's application to reclassify analgesic combinations containing caffeine currently available OTC as prescription-only.
- On 1.7.1998: ibuprofen as an internal analgesic in the higher strength of 400 mg maximum single dose (was 200 mg) and 1 200 mg maximum daily dose (was 800 mg); ketoprofen for external use in analgesic and antirheumatic treatment.
- On 1.1.1999: diclofenac (*Voltaren Emulgel*® - Novartis) as a topical analgesic for a range of conditions including rheumatism (it remained prescription-only for the topical treatment of the inflammation of veins); nedocromil sodium (*Irtan*® and *Tilade*® - Rhône Poulenc-Rorer) nasal spray and eye drops for the treatment and prevention of seasonal allergic rhinitis (hayfever) and perennial allergic conditions. With the switch of diclofenac, most of the major non-steroidal anti-inflammatory drugs (NSAIDs) are available OTC in Germany as topical analgesics for a range of conditions including rheumatism.
- On 1.7.1999: famotidine (10 mg) and ranitidine (75 mg) for the treatment of heartburn.
- On 1.1.2000, the reverse switch to Rx status of procaine and lidocaine for the treatment of arrhythmia. All other approved indications for the two ingredients remained OTC.
- On 1.7.2000, further switches to OTC status for smoking cessation therapy: nicotine gum 4 mg and nicotine sublingual tablets 2 + 4 mg. Coal tar was reverse-switched to Rx.
- On 1.1.2001: ibuprofen liquid (against pain and fever – also for children), terbinafine (against fungal infections) and lufenuron (against flees in dogs and cats).
- On 1.7.2001, ranitidine in liquid formulations (with the OTC indications switched earlier) and fipronil against flees in cats and dogs.
- On 1.1.2002: ibuprofen for rectal application for the treatment of mild and moderate pain or fever; naproxen for the treatment of mild and moderate pain and fever, daily dose up to 660 mg; lodoxamid in eye-drops.
- Recommended for switch on 1.7.2002: nicotine inhaler; naproxen (for mild to moderate pain) in higher dosages (250 mg single dose, 750 mg daily dose and 7500 mg pack size);

icodextrin for peritoneal dialysis; meclofenaminic acid as a veterinary medicine (for use in horses).

In Germany, switches are ingredient related, meaning that all products containing a given ingredient can be sold without a prescription once one product with this ingredient is switched to non-prescription status. The responsibility to decide on classification lies with the Federal Ministry of Health. Although applications can in principle be made by anybody, it is usually the manufacturer who initiates Rx-to-OTC switch applications.

14. PHARMACY TRAINING AND ATTITUDES

Pharmacists are in favour of self-medication insofar as they recognise the ever-increasing significance of this market. Therefore, the German Federal Pharmacist Association (ABDA) encourages 'order' pharmacies to develop into 'customer' pharmacies where pharmacists inform the consumer fully about medicines and their proper use so that the usefulness of self-medication for the consumer is optimised.

Within the undergraduate pharmacy training, German universities deal with OTCs only in a general manner, e.g. as finished medicinal products. There are up to now no separate undergraduate courses on self-medication products. In order to improve the situation in practice, the BAH decided in early 2000 to establish a post-graduate course in "Consumer Health Care" at the famous Humboldt University in Berlin. The course will provide continuous education for pharmacists and economists in particular. The course will especially focus on pharmaceutical management personnel in the marketing, sales and health policy departments. At the end of the course, students will receive additional qualifications. They will be able to analyse marketing and consumer developments and use this knowledge in their respective organisations. The course started in the spring of 2001 (see also point 18).

In the framework of its political work, BAH maintains a lively exchange of opinions and interests with pharmacy associations, both at the federal and the regional (*Land*) level. Moreover, BAH is regularly represented at the annual pharmacy fair 'Interpharm' in Stuttgart, Leipzig and Hamburg.

In June 2000, the German Association of Pharmacists (DAV)– together with the pharmaceutical industry associations BAH and BPI – organised a practice-oriented conference at which all parties examined changes in the German pharmaceutical market. As a result of the government's plans to exclude a large number of medicinal products from reimbursement (see point 9), the self-medication segment of the market is likely to become more important and show increased potential for pharmacists and industry alike. In the meantime, a further well-attended conference took place in Cologne in February 2002.

15. DOCTORS TRAINING AND ATTITUDES

Sick Fund doctors nowadays also support the consumption of non-prescription medicines for a short period of time without the intervention of a medical doctor in case of minor ailments. They increasingly recognise the positive sides of self-medication. Doctors are also providing more and more advice on non-reimbursable products. If paid for by the patient, these medicines do not burden the doctor's prescribing budget. Such forms of doctor-supported or doctor-induced self-medication are a true reflection of the increased prescribing limitations imposed by the government. The 1998 medi*scope consumer research referred to in point

17 showed that 16% of consumers had purchased a self-medication medicine upon a doctor's recommendation and that:

- doctors no longer had the possibility of prescribing a certain product in 24% of cases
- doctors recommended a self-medication product in 51% of cases (up from 44% in 1994)
- patients followed their doctor's recommendation in 76% of cases.

In the university education of German doctors, OTC medicines are only dealt with in the framework of the general training on pharmaceuticals.

In a collaborative effort between BAH, the League of Established German Doctors (*NAV-Virchow-Bund*) and the Federal Association of German Pharmacists (ABDA), seven patient brochures were drafted in 1996-1997 covering the following therapeutic areas: colds; constipation; diarrhoea; vitamins; upset stomach; rheumatic disease; and acne. The brochures were written in a neutral tone agreed by the three associations. 10 000 copies of each of the brochures have since been widely distributed among patients.

In order to be able to meet the requirements of the pharmaceutical market, collaboration with doctors is considered of equal importance as collaboration with pharmacists.

16. RELATIONS WITH CONSUMER ASSOCIATIONS/PATIENT GROUPS

Concerning relations with consumer associations and patient groups, BAH reports that there is cooperation with these associations and that there are no fundamental differences of opinion. The attitude of consumer groups towards self-medication can in general be characterised as positive.

17. CONSUMER ATTITUDES/RESEARCH

A regular series of consumer research on attitudes towards self-medication was launched by BAH in 1986 and repeated in 1990 and 1994 among 2 500 persons. The research, which was carried out by *I+G Gesundheitsforschung*, showed in 1994 that the number of households buying OTCs in pharmacies increased from 78% in 1990 to 89% in 1994 in West Germany and from 79% to 85% in East Germany.

The amounts spent on OTC products rose from DEM 18 to DEM 23.37 in West Germany and from DEM 8.90 to DEM 21.37 in East Germany. People in both parts of the country spent an equal proportion of their income on OTC medicines (including herbal medicines).

Although the majority of consumers follow the instructions, about one third found them unclear. This was interpreted as a clear message for better consumer information.

The research also showed that, in economic terms, the income elasticity of preventive products (vitamins, minerals and natural mineral water) was greater than that for therapeutic medicines, meaning that the demand for this type of products was higher in West Germany.

In 1998, this regular consumer research took the form of two modules within the research company's medi*scope and medic*health studies and was expanded to include 10 000 persons. The main outcomes of the 1998 survey were that:

- Within the six months of the survey, around 39 million people (or 62% of the German population over 15) self-medicated, i.e. took measures on their own responsibility with non-prescription medicines to maintain health or to treat minor ailments.

- Around 31% of the population regularly use self-medication products such as vitamins and minerals, tonics, garlic products and immunity boosters for health maintenance and sickness prevention, making a considerable contribution to public health and alleviating the state healthcare budget.
- Knowledge about medicines is increasing all the time, forming a solid basis for the appropriate use of medicines under one's own responsibility. In West Germany 66% (7% more than in 1994) found that they are well or very well informed about medicines. For East Germany, the figures were 61% (against 52% in 1994).
- 84% (West: +3%) and 81% (East: +5%) ask for self-medication products by trade name, showing increasing brand loyalty and brand satisfaction.
- Although the number of products purchased as a result of pharmacist recommendation has slightly decreased, there was a marked increase in the number of pharmacist consultations to around 50% of purchase acts.
- The number of self-medication products bought upon the recommendation of a doctor has increased from 13% in 1994 to 17% in 1998 in West Germany, and from 12% to 14% in East Germany. This increase can partly be explained by the increased co-payment levels since 1.7.1997.
- The patient leaflet remains an important source of information on self-medication products. The number of persons declaring they rarely or never read the leaflet has decreased from 13% (1994) to 8% (1998) in the Western part and from 14% to 10% in the Eastern part of Germany.
- Annual household spending on self-medication increased from DEM 279.50 in 1994 to DEM 318.00 in 1998 (+14%). Higher co-payment costs already represent an annual increase of DEM 60.00 on the private health costs budget.

The fifth survey concerning health-political expectations of the German population carried out by *Gesellschaft Pharma-Informationssysteme* (GPI) in Nuremberg and presented in the fall of 2000 showed that:

- There is a need for further reforms in the health care sector, in order to avoid a two-class medicine system.
- People prefer a higher co-payment than further reductions of reimbursed health services.
- People want to have more possibilities to choose different service packages within the social health insurance (SHI) and the re-payment of fees if services have not been used.
- Instead of the current budget for medicinal products, people prefer a wider use of self-medication.
- Self-medication is the right concept to achieve cost-reduction in the social health insurance system. More than 75% of interviewees said that they are able to practise more self-medication after using pharmacist recommendations.
- A high co-payment for medicinal products could lead to more cost-awareness and to a higher degree of compliance.
- The most effective way to improve self-medication is the establishment of a self-medication budget. This means that insurance companies would reimburse the insured at the end of the year for all non-prescription medicines they have directly bought without a prescription in pharmacies. Ultimately, a self-medication budget will have cost-reduction effects for the insurance companies because there will be no charges for fees from prescribing doctors.

18. OTHER NATIONAL DEVELOPMENTS

The BAH decided in early 2000 to establish a post-graduate course in "Consumer Health Care" at the famous Humboldt University in Berlin. The course will provide continuous education for pharmacists and economists in particular. It will teach interdisciplinary basic knowledge such as, e.g.:

- the legal basis for consumer health care
- the consumer as target of consumer health care
- communication and consumer health care
- health management and self-medication
- pharmacoeconomics
- disease management
- ethical aspects of medicines care
- telecommunication, etc.

The course will especially focus on pharmaceutical management personnel in the marketing, sales and health policy departments. At the end of the course, students will receive additional qualifications. They will be able to analyse marketing and consumer developments and use this knowledge in their respective organisations. The course started in the spring of 2001.

19. ELECTRONIC INFORMATION

BAH makes several types of association activity data available on its website. Data include recent market figures, price communications, publications and announcements of seminars organised by the BAH Scientific Service (BAH-WiDi). In February 2000, BAH installed newly designed webpages on the Internet. The new pages offer complete information on all aspects of the pharmaceutical market in Germany on www.bah-bonn.de.

The BAH-internet portal for non-prescription medicines (www.arzneimittelscout.de) went online in June 2001. After selecting indications of interest, all relevant sub-indications are shown as well as general information on this indication / sub-indication. The next page shows all non-prescription medicines to treat this indication / sub-indication. With the next click, the user can choose a non-prescription medicine from a product description with pack-shot. The user can then be linked directly to the homepage of the manufacturer for further information and advice. The concept also contains information on pharmacies countrywide pharmacies on weekend and/or night duty as well as a list of all BAH-member companies. Further services for the consumer are offered by a rubric dealing with healthcare advices, general information on self-medication and the offer to consult a pharmacist by e-mail for advice.

The portal now includes more than 700 non-prescription medicines and is therefore representative of the non-prescription market in Germany. Since its launch, the site has allowed more than 3 million pages to be printed, showing that the portal is a highly accepted tool for consumers to get information on non-prescription medicines and an ideal platform for industry to communicate with the consumer. BAH partners Internetzentrale, ABDA, Wetter-Online, Lifeline and many others are contributing to this success by promoting the portal.

20. AESGP MEMBER ASSOCIATION

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