Accelerated Market Access of Medicinal Products after October 2005 - A Survey of the Challenges in the updated EU Pharmaceutical Legislation

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List of Abbreviations

AR	Assessment Report
CD	Commission Decision
CDD	Commission Draft Decision
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional Marketing Authorisation
CMD (h)	Co-ordination Group for Mutual Recognition and Decentralised Procedures for Human Medicinal Products
CMS	Concerned Member State
CMSs	Concerned Member States
COMP	Committee for Orphan Medicinal Products
CTD	Common Technical Document
CP	Centralised Procedure
CVMP	Committee for Medicinal Products for Veterinary Use
DP	Decentralised Procedure
DAR	Draft Assessment Report
EEA	European Economic Area
EC	European Commission
EEC	European Economic Community
EU	European Union
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
ERP	European Reference Product
FAR	Final Assessment Report
FUM	Follow-up Measure
HMA	Heads of Medicines Agencies
HMP	Herbal Medicinal Product
HMPC	Committee for Herbal Medicinal Products
ICD 10	International Classification of Diseases 10
INN	International Non-proprietary Name
MA	Marketing Authorisation
MAs	Marketing Authorisations
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MRI	Mutual Recognition Index
MAP	Marketing Authorisation Procedure
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure

MP	Medicinal Product
MPs	Medicinal Products
MS	Member State
MSs	Member States
NtA	Notice to Applicants
NCE	New Chemical Entity
NCA	National Competent Authority
LE	Line Extention
OMP	Orphan Medicinal Product
PAR	Public Assessment Report
PDCO	Paediatric Committee
PIL	Patient Information Leaflet
PIM	Product Information Management
PrAR	Preliminary Assessment Report
QRD	Quality Review of Documents Group
RMP(RM)	Reference Medicinal Product (reference product)
RMS	Reference Member State
RSI	Request for Supplementary Information
SA	Scientific Advice
SME	Small and Medium-sized Enterprise
SRP	Simplified Registration Procedure
SmPC	Summary of Product Characteristic
SO	Specific obligation
SOP	Standard operating procedure
WHO	World Health Organisation

Foreword

The idea for this book was originally born in 2004/2005 during the preparation of a master thesis in the framework of postgraduate course on "Drug Regulatory Affairs" leading to a master's degree set up at Rheinische Friedrich-Wilhelms Universitaet, Bonn, in co-operation with the German Association of Drug Regulatory Affairs (DGRA), at a time when the EU pharmaceutical legislation changed significantly. While providing a summary of the development of the legislation which will be of special interest to those readers, who are new in the field of drug regulatory affairs as it explains how and why the system changed over time. It compiles information on the different marketing authorisation procedures for pharmaceuticals in the EU with a focus on the potential for accelerating market access. This book has been prepared on the grounds of the current legislative documents, regulations, directives, reports and guidelines and provides an overview of the authorisation system with respect as to how different pharmaceutical products can be placed on the EU market.

Following the Review of the pharmaceutical legislation in 2004, important conditions regarding the accelerated market access came into force in the EU offering a number of new opportunities to the pharmaceutical industry and regulators, and, at the end of the day, to the patient. However, in order to make best use of these new provisions, the potential user is faced with the absence of a single document which highlights the important issues and aspects in this area. The procedures relating to pharmaceuticals are spread out in many legislatively binding and hundreds of unbinding documents, reports, guidances and guidelines, which are, on the one hand, very difficult to follow and, on the other hand, are being updated on an ongoing basis. This book is, therefore, intended to provide guidance and a key to where to find the necessary detailed information.

It will be helpful for beginners in the field of regulatory affairs and for all those who would like to gain a better understanding of the EU pharmaceutical legislation and the different licensing procedures, an area where it might be found difficult to read and follow a large number of EU documents. As a manual, it will be of help to those studying the complicated area of regulatory affairs, a mixture of many scientific and legal procedures, in order to receive a concise overview as to how to apply these adequately and to understand exactly which important sources of information to use and where to find the details.

The authors

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Summary

The marketing authorisation procedures for medicinal products have been gradually developed since 1965 and are still subject to optimisation and changes to meet new requirements and raised challenges. The current system is based on four separate procedures for receiving a marketing authorisation for a medicinal product: centralised, decentralised, mutual recognition and solely national.

The Centralised Procedure (CP) is mandatory for certain medicinal products developed by means of biotechnological processes and for new active substances in specific therapeutic indications. Regulation (EEC) No 2309/93 which entered into force in 1995 introduced the Centralised Procedure and was subsequently revised by Community Regulation (EC) 726/2004, which has partly been in force since May 20, 2004 (Title IV), while the remaining titles only came into effect on 20 November 2005.

For those medicinal products not falling under the mandatory scope of the Centralised Procedure, the EU system provides the **Mutual Recognition Procedure (MRP)**, which has been introduced on the basis of Council Directive 93/39. For situations where an applicant intends to market a medicinal product in one Member State (MS) only, there is still the option to apply for a solely National Marketing Authorisation in this particular Member State. Directive 2004/24/EC and Directive 2004/27/EC, which amend or change the existing Community Code - Directive 2001/83/EC - have come into effect as of October 30, 2005 and introduced the Simplified Procedure for herbal and homeopathic MPs and the new Decentralised Procedure.

In the **Decentralised Procedure (DP)** the applicant is again free to choose the EU Member State that will act as the Reference Member State (RMS). Harmonisation of both procedures - DP/MRP, concerning the Summary of the Product Characteristic (SmPC) and PIL is in force among all MSs parallel with the Assessment Report (AR). Now, the Decentralised Procedure (240 days) has advantages to the previous MRP (420 days) not only with respect to the shorter period of 180 days (equivalent to a 42% reduction in the time needed) in the Reference Member State (RMS) and Concerned Member States (CMSs) phase, but also in the arbitration process due to the efforts of the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMD (h)) in case of reaching consensus within 60 days. The updated MRP, where claims of “potential serious risk to public health” are raised, will also profit in the same way from this new activity of the CMD (h), which has replaced the informal Mutual Recognition Facilitating Group (MRFG) of the Heads of Medicines Agencies.

For the **Simplified Registration Procedure**, which is known as "traditional-use registration", traditional use for 30 years should be demonstrated including at least 15 years in the Community. The new EMEA **Herbal Medicinal Products Committee** will be a key element in the new regulatory environment for herbal products in the EU and it may provide major clarifications from a regulatory point of view through the establishment of monographs and lists for herbal medicinal products. The transitional period for herbal medicinal products till 2011 is also an opportunity to allow products existing on the market to continue to accumulate evidence of usage in the EU. Overall, by 2011 all herbal medicinal products will have to be licensed/registered in order to stay on the market.

The aim of this study is to survey the EU pharmaceutical legislative frame for intellectual property protection, of the marketing authorisation procedures and arbitrations in the current legislation, Review 2005, with the previous Community law to estimate whether procedures for accelerated market access of medicinal product approvals are available.

The results of comparative analyses show many advantages that have been introduced in the new Review 2005 compared to the former pharmaceutical legislation. The new legislation facilitates the access to the European market for both innovative and generic products. It especially provides substantial improvements in the generic and innovative area, in particular by introducing many new terms and issues: definition of generic, reference medicinal products, and biosimilar.

Harmonisation of the 10-year marketing protection period is introduced in the EU Pharmaceutical law. The new period of exclusivity provision will only be applied to reference medicinal products whose marketing authorisation applications are submitted after the new provision has come into force. The reality is that the generic industry will profit from the "eight-year provision" not earlier than 2013 because the last date for the directive transposition is October 2005. In real life, at least part of the two years of earlier generic submission before expiration of the marketing protection of the reference product will be used for the evaluation of the submitted generic dossier. However, this will still give the opportunity for an accelerated launch of generics.

The scope of the **Community procedure** is also enlarged with a number of new indications, e.g. acquired immune deficiency syndrome, cancer, diabetes, neurodegenerative disorders. In addition, the possibility to receive marketing authorisations for generic versions of a reference product authorised by the Centralised Procedure through the Mutual Recognition Procedure is now available. In addition to the specific marketing authorisation of medicinal products in exceptional circumstances in force in the previous Community law, new temporary marketing authorisations **"Conditional Authorisation and**

Compassionate use" with incomplete dossiers as regards non-clinical and/or clinical studies but with a positive risk/benefit balance based on early evidence and annual reassessment for a rapid availability of innovative medicines for patients, are already possible.

The legislative pharmaceutical documents in force since autumn 2005 are focused on the **Centralised accelerated assessment procedures** (217 days), which is by 60 days (22%) shorter than the current standard CP (277 days). Concerning the duration of the assessment in the CP, the current deadline of 210 days **could be reduced down to 150** days in case of an Accelerated Procedure. The period till the Commission Decision (CD) becomes by 36 days shorter than in the previous legislation (41%, from 88 to 52 days). Now the time for the Commission Decision is absolutely fixed, 15 days, in contrast with the previous legislation, where that period of time was not limited and legislatively fixed.

In general, the Review 2005 attributes particular attention to the implementation of provisions reinforcing the safety of medicines, accelerating the access of medicines to the EU market and availability to the patients, respectively. Thanks to the network and the activities between the EMEA and the more than 42 national competent authorities (NCAs) in the EU, the implementation of the amended legislation in late 2005 will be optimised in order to meet all new pharmaceutical challenges in the enlarged EU.

1. Introduction

1.1. Background of the legislative health and pharmaceutical framework of the EU

The European Economic Community was founded after the Second World War to bring the European nations closer together and establish an economic basis for peace and public stability for the generations. In the meantime, the Community has grown larger and more countries have been gradually involved. However, the same institutions still form the constitutional framework within which the Member States work towards the closer union envisaged by its founders. In the early years, the Commission would decide and the Court of Justice would interpret. In May 1949, the European Council with members from ten countries was founded with the main idea of European countries convergence. (1)

The **1957 the Treaty of Rome empowered** the European Parliament only to deliver opinions on European Commission proposals for legislation under the "consultation" procedure. Decisions were taken by the Council of Ministers, which was not obliged to take these opinions into account. The most important provision regarding medicinal product law was Article 100, which regulated the creation of harmonising directives in order to realise the internal market. (2)

Following the **Treaty of Amsterdam (1997)** that entered into force **on 1 May 1999,** some significant institutional changes in the role of the European Parliament were made as a genuine co-legislator with the Council, which was recognised by streamlining the co-decision procedure and extending the areas to which it applies. Overall, the number of procedures by which Parliament helped to shape legislation was reduced to three, i.e. co-decision, assent, and consultation. Parliament was also empowered to make proposals for its own electoral procedure based on principles common to all Member States. The health Article 100 of the Rome Treaty was replaced by Article 95 in the **Treaty of Amsterdam (1997)** as the basis of harmonising directives aimed at the Member States. The directive, which is based on Article 95, has been established in co-operation between the European Parliament and the Commission and the Council, following the so-called "***Co-decision procedure"***, in which the member state governments were represented at ministerial level. Such directives are the highest level of legislation in the EU. (3,4)

The **Single European Act gave Parliament** more say in the drafting of Community legislation by introducing the "***Co-operation procedure***". However, the Council still had the final word. Under the "co-decision" procedure introduced by the Treaty of Maastricht and revised by the Treaty of

Amsterdam, no draft text can become a law without the formal agreement of both Parliament and the Council. In other words, as far as the procedure is concerned, these two European institutions are now on an equal footing. (5)

The Single European Act (1986), the Treaty on the European Union (Maastricht Treaty, 1992) and the Treaty of Amsterdam (1997) have changed the work of the European Union and extended its remit beyond purely economic matters to encompass public health, social policy, research, consumer, and environment protection. (3,5,6)

The new **Treaty establishing a Constitution for Europe** (2004) is putting more emphasis on repeating that the organisation and financing of health systems are both within the competence of the Member States. One of the tasks of the Community is to establish a common market and a monetary union to promote throughout the Community a harmonious, balanced, and sustainable development of economic activities, high level of social protection, raising living standard and quality of life, social cohesion, and solidarity accross the Member States. (7)

The Single European Act introduced areas of health-related work such as a large-scale research programme as well as the development of health and pharmaceutical legislation. The position of the **Treaty establishing a Constitution for Europe, Article 278** in the Section of public health replaces **Article 152** of the **Treaty of Amsterdam,** where public health is an "Action by the Union, which shall complement national policies, shall be directed towards improving public health, preventing human illness and diseases, and obtaining sources of danger to physical and mental health". This article envisaged high standards of quality, safety of organs and substances of human origin, blood and blood derivates, a measure setting high standards of quality and safety for medicinal products and devices for medical use. In the new version of Article 278 of the **Treaty establishing a Constitution for Europe,** the fight against the major health scourges is focussed by promoting research into their causes, their transmission, and their prevention, as well as health information and education. (3,5,7,8)

The internal market is one of the cornerstones of the European Union, a result of the **Treaty establishing the EEC (Treaty of Rome),** which envisaged the establishment of a "common market" based on free movement of goods, persons, services, and capital. In the term free movement of goods, specific legislation has been developed concerning the products related to the health sector. The good Community pharmaceutical legislation resulted in the accepted requirements and provisions for free circulation till today. (6)

In order to remove obstacles to the internal market of pharmaceuticals while at the same time ensuring a high level of public health protection, the Community has gradually developed a harmonised legislative framework for

medicinal products since 1965. Very soon after the introduction of the **Treaty of Rome in 1957**, which created the EEC legislation on medicinal products, Directive 65/65/EEC was published. The direct cause for the development and implementation of the first Directive in 1965 was the drama with a medicinal product containing thalidomide, which – due to its ability to prevent morning sickness – was especially prescribed as a mild sedative and sleeping pill during the first three months of pregnancy. The First Medicinal Product Directive 65/65/EEC was applied to proprietary medicinal products, which were industrially manufactured and were known as branded medicinal products. (see Table 1). (2,9)

The European Economic Community (EEC) was to a great extent concerned with pharmaceuticals due to the fact that a large internal market for these products is required and the health of the citizens must be protected against poor quality medicinal products. During the more than 40 years of developing the EU pharmaceutical legislation, many legal and regulatory documents have been introduced and improved. In general, the public pharmaceuticals policy requires robust regulations, motivations of competitiveness, innovative medicinal products, and a balance between the innovative and generic industry with the focus on the public health of the patients.

1.2. Aims and scope of the EU Pharmaceutical Policy and Law

Since 1965, medicinal products (MPs) can only be placed on the market in the European Community once they have been granted a marketing authorisation. Marketing authorisation procedures have been gradually developed since 1965 and are still subject to optimisation and modifications to meet new requirements and challenges. (Table 1)

The current system is based on four separate procedures for granting a marketing authorisation for a medicinal product.

The Centralised Procedure is mandatory for certain medicinal products developed by means of biotechnological processes and for new active substances in specific therapeutic indications. In addition, it is optional for certain other categories of medicinal products such as those containing new active substances not authorised in the Community at the time of coming into force of the Regulation (EC) 726/2004 and those medicinal products presented for an entirely new indication constituting a significant innovation. The Centralised Procedure leads to a single marketing authorisation (MA) valid throughout the whole Community granted after Commission decision and based on a scientific evaluation by committees created within the European Medicines Agency for the Evaluation of Medicinal Products (EMEA). **Regulation (EEC) 2309/93,** which entered into force in 1995, introduced the Centralised Procedure and was

Table 1. Development of the EU Pharmaceutical legislation for human medicinal products from 1965 end 2007

Year Publ.	Legislative Document	Topics covered by the legislation	Sources of publication
1965	Council Directive 65/65/EEC	MA requirements for quality, safety, efficacy	OJ L 22, 9 Feb 1965, p. 3
1975	Council Directive 75/318 Council Directive 75/319 Council Directive 75/320	Admission requirements Action for proprietary MP and Committee Rules for Pharmaceutical Committee	OJ L 147, 9 June 1975, p. 1 OJ L 147, 9 June 1975, p. 13 OJ L 147, 9 June 1975, p. 23
1978	Council Directive 78/25/EEC:	for colouring substances	OJ L 011, 14 Jan 1978, p. 18
1983	Council Directive 83/570	Administrative action relating to proprietary medicinal products	OJ L 332, 28 Nov 1983, p. 1
1987	Council Directive 87/19/EEC, Council Directive 87/21/EEC Council Directive 87/22/EEC	Amended Dir. 65/65/EEC Data exclusivity for innovative MP For placing high-technology MP, derived from biotechnology	OJ L 015, 17 Jan 1987, p. 36 OJ L 021, 23 Jan 1987, p. 78 OJ L 015, 17 Jan 1987, p. 38
1989	Council Directive 89/105/EEC, Council Directive 89/341/EEC Council Directive 89/342/EEC Council Directive 89/343/EEC Council Directive 89/381/EEC	Pricing and Reimbursement of MP Administrative action to proprietary MP Immunological provision for MP Provisions for radiopharmaceuticals Provision for MP - human sources	OJ L 40, 11 Feb 1989, p. 8 OJ L 176, 23 June 1989, p. 55 OJ L 142, 25 May 1989, p. 14 OJ L 142, 25 May 1989, p. 16 OJ L 181, 28 June 1989, p. 44
1991	91/356/EEC	GMP principles for MP	OJ L 195, 17 July 1991, p. 30
1992	Council Directive 92/25/EEC Council Directive 92/26/EEC Council Directive 92/27/EEC Council Directive 92/28/EEC Council Directive 92/73/EEC	Wholesale distribution of MP Classification of MP Labelling, package leaflet of MP Advertising of MP	OJ L 113, 30 April 1992, p. 1 OJ L 113, 30 April 1992, p. 5 OJ L 113, 30 April 1992, p. 8 OJ L 113, 30 April 1992, p. 13
1993	Council Regulation (EEC) 2309 Council Directive 93/39/EEC Council Directive 93/41/EEC	Establishment of EMEA and CP Establishment of MRP High-technology MP, derived from biotechnology	OJ L 214, 24 August 1993, p. 1 OJ L 147, 24 August 1993, p. 22 OJ L 214, 24 August 1993, p. 40
1995	Com. Regulation (EC) 540/95, Com. Regulation (EC) 541/95	Variations CP Variations - MRP	OJ L 55, 11 March 1995, p. 5 OJ L 171, 21 July 1995, p. 46
1999	Com. Regulation 1999/82/EC Com. Regulation 1999/83/EC	Testing of medicinal products Amended "well established use"	OJ L 243, 15 Sep 1999, p. 7 OJ L 243, 15 Sep 1999, p. 9
2000	Directive 2000/38/EC Regulation (EC) 141/2000 Com. Regulation (EC) 847/2000	Administrative action relating to MP Orphan medicinal products Designation criteria of orphan MP	OJ L 139, 10 June 2000, p. 28 OJ L 018, 22 Jan 2000, p. 1 OJ L 103, 28 April 2000, p. 5
2001	Directive 2001/20/EC Directive 2001/83/EC	Clinical Trials Directive Codification of the EU human pharmaceutical directives	OJ L 121, 01 May 2001, p. 34 OJ L 311, 28 Nov 2001, p. 67
2003	Commission Directive 2003/63/EC Regulation (EC) 1084/2003 Regulation (EC) 1085/2003	Replaced Annex I of D. 2001/83/EC Variations MRP Variations - CP	OJ L 159, 27 June 2003, p. 46 OJ L 159, 27 June 2003, p. 1 OJ L 159, 27 June 2003, p. 24
2004	Regulation (EC) 726/2004 Directive 2004/24/EC Directive 2004/27/EC Directive 2004/98/EC	EMEA, Centralised Procedure Herbal Medicinal Products Data Exclusivity -MRP/DP Blood Products	OJ L 136, 30 April 2004, p. 1 OJ L 136, 30 April 2004, p. 34 OJ L 136, 30 April 2004, p. 34 OJ L 136, 30 April 2004, p. 34
2005	Commission Directive 2005/28/EC Commission Regulation 2049/2005	GCP, manufacturing and import-IMP Financial and administrative provisions for SMEs	OJ L 91, 9 April 2005, p. 13 OJ L 329, 15 Dec 2005, p. 4
2006 2007	Regulation (EC) No 1901/2006 of Regulation (EC) No 1902/2006 of Regulation 658/2007	on MP for paediatric use on MP for paediatric use financial penalties for infringement MP	OJ L 378, 12 Dec 2006, p. 1 OJ L 92, 20 Dec 2006, p. 20 OJ L 92, 14 June 2007, p. 10

subsequently replaced by **Community Regulation (EC) 726/2004.** (10,11)

For those medicinal products not falling under the mandatory scope of the Centralised Procedure, the EU system provides the Mutual Recognition Procedure (MRP), which has been introduced on the basis of **Council Directive 93/39,** Article 7, which amended the Council Directive 65/65/EC. The Mutual Recognition Procedure is to be used by the applicant whenever an application for marketing authorisation for a medicinal product is intended in at minimum another Member State (MS) with a national marketing authorisation already having been granted for one Member State. Later, as from 30th of October, with the **Directive 27/2004/EC** of the European Parliament, a Decentralised Procedure (DP) was introduced in order to give an opportunity to applicants to file for a parallel marketing authorisation in more than one MS without a previous national MA. For those situations where an applicant intends to market the medicinal product in one Member State only, there is still the option to apply for a solely National Marketing Authorisation. (9,12,13)

Regulation 2309/93, Article 71, obliged the Commission to publish a report on the experience acquired as a result of the operation of the centralised and the mutual recognition authorisation procedures (set out in Chapter III of Directive 75/319 and in Chapter IV of Directive 81/851 and Council Directive 93/39) within six years after the entry into force of the Regulation. (10)

In order not to neglect any aspect and to get an accurate and objective view of the system taking into account all proposals of national authorities, industry, patients, and healthcare professionals, the Commission commissioned an independent company which prepared a report **"Evaluation of the operation of Community procedures for the authorisation of medicinal Products**" and based on that report the European Commission published a review on the experience acquired in the application of marketing authorisation procedures under Regulation 2309/93/EEC, Chapter III of Directive 75/319/EEC, and Directive 87/22/EEC - report made under article 71 of Regulation 2309/93/EEC - COM (2001) 606 final of 23 October same year. (14,15,16)

The "**Commission's review of the pharmaceutical legislation**" from January 2001 concluded that the system in place since 1995 works well and has contributed to achieving a high level of public health protection as well as progressing the internal market in pharmaceuticals in Europe. However, the Commission has summarised in its report that there is a need to adapt certain marketing authorisation provisions in Regulation 2309/93 and the Codes on human and veterinary medicines to the recommendations in that report. (17)

These intrinsically linked goals can be optimally realised only if the review achieves a sound overall equilibrium between all of them. This requires a balance between the centralised and decentralised systems of medicinal

product authorisation since the same fundamental objectives, namely to ensure a high level of public health protection and to contribute to the completion of the internal market in medicinal products, have been applied to both procedures. The revision of the system follows the same objectives as the government legislation since 1965, namely the reinforcement of measures to support the competitiveness of the European-based pharmaceutical industry in the context of the increasing globalisation of this sector and the enlargement of the European Union by 10 Member States on 1st of May 2004 and by Bulgaria and Rumania on 1st of January 2007. (18)

After the first Commission Report in 2001 for the procedures authorising the medicinal products in the Community, many new proposals for establishing a robust pharmaceutical legislation have been developed. The Commission's objective was to implement these proposals resulting in various new legislative documents in the period 2001-2005**.** These proposed revisions of the pharmaceutical legislation consisted of proposals for a regulation and a Community Code (Directive 2001/83/EC) based on all previous pharmaceutical Directives. (19)

Many new aspects of the new pharmaceutical legislation came into force in 2003 and 2004, especially to accommodate the EU enlargement, while additional fundamental changes to the European regulatory system took first effect in late 2005. (see Table 1)

Regulation (EC) 726/2004, which replaced Regulation (EEC) No 2309/93, has partly been in force since May 20, 2004 (Title IV), while the remaining titles only came into effect on November 20, 2005**.** In this regulation, particular attention is attributed to the implementation of provisions reinforcing the safety of medicines, accelerating the access of medicines to the EU market, and availability to the patients, respectively. High importance will be attributed to initiatives aimed at increased transparency, communication, and provision of information to patients, healthcare professionals, and the general public. (10,11)

Directive 2004/24/EC and **Directive 2004/27/EC**, which amend or supersede the existing Community Code - Directive 2001/83/EC - have come into effect as from October 30, 2005. Directive 2004/27/EC introduced the new Decentralised Procedure and updated the Mutual Recognition Procedure of 1998. Directive 2004/24/EC regulates the provisions for homeopathic and herbal products where a Simplified Registration Procedure was introduced and a new committee for herbal medicinal products (HMPC) was established at the EMEA. (13,18,19,20)

The **Work Programme for the European Medicines Agency 2005** was focussed on the preparation for full implementation of the new legislation coming into force in November 2005. Special emphasis was given to the implementation of the legislative provisions and the creation of the right environment to

stimulate research of innovators and to support small and medium-sized enterprises. These initiatives include implementation of the concept of risk management plans, expansion of the scope of medicines to be authorised through the centralised procedure, and establishment of the accelerated authorisation procedure. (21)

In order to strengthen and accelerate EMEA's activities for the implementation of the legislative requirements, an "Implementation Task Force" programme started at the January 2004 CPMP session. Monthly progress reports of this CHMP/EMEA Implementation Task Force (CEITAF) have been published as part of the monthly CHMP reports since January 2005. (22)

The legislative pharmaceutical documents in force since autumn 2005 are focused on **accelerated assessment procedures**, **conditional authorisation, and compassionate use** procedures for a rapid availability of innovative medicines for patients in the EU.

In addition, the offered new possibilities for generic products provide the choice to the applicant to select between the Centralised and the Mutual Recognition Procedure for generics to centrally authorised products which do not fall under the mandatory scope of the CP in the Annex of regulation 2004/726/EC. In parallel with the newly introduced Accelerated Procedure at EMEA, where the centralised system includes a new accelerated assessment within 150 days and additional new specific procedures, a Conditional Marketing Authorisation (CMA) and a Compassionate Use procedure have been established. At Member States' level, the new decentralised procedure for marketing authorisation is in force as of 30 October 2005. (11)

Simplified registration procedures for homeopathic and herbal medicines provide new advantages for MPs in terms of their rapid market access. However, all these procedures have their challenges till sufficient experience and knowledge will have been accumulated in the different Member States throughout the Community. (20)

In addition to legislative challenges, the Agency is also facing rapid development in the field of science and technology, as well as recent changes in the political environment. In order to fully embrace the opportunities presented, the Agency, in addition to the implementation of the new legislation, also stated their intention to implement a number of actions originating from the Agency's **Road Map to 2010.** The actions fall within a number of areas including revision of the current procedural framework for the evaluation of medicines, e.g. the different procedures and increased level of scientific support, reinforcement in the area of supervision and safety of medicines, initiatives to improve transparency and provide clear and understandable information to patients, healthcare professionals and public and international collaboration. Initiatives outlined in the EMEA's Road Map coupled with the implementation

of the new pharmaceutical legislation further contribute to the reinforcement of an effective and robust European regulatory system. Further, to complete the internal market of pharmaceuticals and to establish a stable regulatory framework favourable to the competitiveness of the European pharmaceutical industry while taking into consideration the aspects of the globalisation, the next Agency's report following the Road Map to 2010 is planned to be finished in five years in order to summarise the experience for the period of time. (24)

1.3. Main objectives of this survey

- To survey the regulatory frame of the data exclusivity period of medicinal products in terms of accelerated market access in the EU before and after end 2005.
- To survey the regulatory frame of the marketing authorisation procedures (MAPs) of medicines which lead to accelerated market access in the EU in comparison with the previous MAPs before 2005.
- To survey the regulatory frame of the arbitration procedures introduced in 2005, compared to the previous arbitration procedure of medicines in EU.

1.4. Methodology of the survey

- Comparative analysis of the data exclusivity period in the current legislation, Review 2005, with the data exclusivity period in the previous Directive 2001/83/EC and Regulation (EEC) 2309/93. (10,19)
- Comparative analysis of the centralised procedure for marketing authorisation of medicines in the current legislation, Review 2005, with the centralised procedure for marketing authorisation of medicines in Regulation (EEC) 2309/93. (10, 11)
- Comparative analysis the of the decentralised system for marketing authorisation of medicines in the current legislation, Review 2005, with the decentralised system for marketing authorisation of medicines, including herbals and homeopathics in Directive 2004/24/EC, 2004/27/EC. (13, 20)

Analysis and Discussion

2. EU regulatory framework of data exclusivity protection of medicinal products before and after 2005

In Europe, national and EU regulators have considered data exclusivity to be introduced in 1987 by Council Directive 87/21/EEC. The rules on the data exclusivity period have been changed in the new EU pharmaceutical laws enacted in late 2005 which brings important changes in this area of drug legislation that have significant influence and notable effect on the data exclusivity process of reference products (RP) in the EU. (25,26)

2.1. Definitions and conditions simplifying the "data exclusivity" process

The data exclusivity system for medicinal products is completely independent of intellectual property laws. Data exclusivity was introduced, because the legislators decided that the methods of protecting research which were available to the pharmaceutical industry were insufficient. Data exclusivity was introduced to prevent the development of innovative medicinal products from being hindered for a certain period of time, where the patent legislation, when the product was placed on the market, had not yet been introduced. After the period of time has expired, the dossier becomes "open" and other applicants may refer to it. As a rule, a patent for a new substance is valid for 20 years and product development and the compilation of the registration dossier generally takes 12-16 years on average and the patent protection will expire during the period when the dossier is closed. Therefore, data exclusivity is an important instrument for the pharmaceutical industry to ensure return on investment for innovative medicinal products. Data exclusivity was provided in Article 10 (1) (a) of Directive 27/2004/EC which amends Directive 2001/83/EC. (13,19)

2.1.1 Definition of "reference medicinal product" and "generic medicinal product"

The term "essentially similar" is defined in Directive 2003/63/EC amending the annex of Directive 2001/83/EC to incorporate the Common Technical Document (CTD). The legal concept for an "essentially similar" medicinal product is based on the decision of the European Court of Justice

(ECJ, Case 368/96), the Generic UK Case from 1998 and has been subsequently introduced into the updated Annex of 2001/83/EC, which has become today Directive 2003/63/EC Part II, 2b. (27,28)

In Directive 2004/27/EC, Article 10.2 clarifies the terms **"reference medicinal product"** and **"generic medicinal product"** and for the first time in the European pharmaceutical legislation provides such definitions. Both Directives 2003/63/EC and Directive 2004/27/EC have been published in 2003 and 2004 respectively, and therefore the term "essentially similar" is still included in the Directive 2003/63/EC.

The term "essentially similar medicinal product" in Directive 2003/63/EC, Part II, 2b, includes the term "generic product" but in Article 10b of Directive 2004/27/EC the term "essentially similar product" is not introduced and that could lead to different explanations and misunderstanding when both directives are used, as the terminology of these documents is not identical. (26,27,29).

2.1.2 Definition of "line extension" and the concept of "global marketing authorisation"

A definition of the term "line extension" and the notion of the "global marketing authorisation" have been explicitly introduced with the changes in the pharmaceutical legislation in late 2005. The applicant can supply additional information "providing proof of the safety and/or efficacy of salts, esters, or derivatives of the authorised active substance" in order to obtain an authorisation of a medicinal product containing such a modified active substance as a generic medicinal product (Dir. 2004/27/EC Article 10.2(b)). Introduction of the principles outlined in the same Directive is a very important step because the various immediate-release oral pharmaceutical forms are to be considered as the same pharmaceutical form according to Article 6 of Directive 2001/83/EC, as amended. When a medicinal product has been granted an initial marketing authorisation, any subsequent additional forms, administration routes, presentations, variations and extensions shall be considered as belonging to the same "global marketing authorisation" and they are not covered by an additional data exclusivity period.

No legal issue on the various immediate-release oral pharmaceutical forms existed till Directive 2004/27/EC. The explanations in that direction were based only on the Notice to Applicants (NtA), Volume 2A November 2005, Revision 3 - ENTR/F2/BL D(2002), following the European Court of Justice Case (29 April 2004 - Novartis, C-106/01), (See Table 2). Modified release products or other dosage forms as line extensions according to Article 10 (2) (a) of Directive 2001/83/EC, as amended by Directive 2004/27/EC, of an existing marketing authorisation are not protected by a separate exclusivity period. (13,26)

2.1.3 Market Obligation of the reference medicinal product. European reference medicinal product (ERP)

Another important step is that Article 10.1 in Directive 2004/27/EC, respectively Article 10 (1) in the consolidated Directive 2001/83/EC, ***removes the obligation for the reference medicinal product to be on the market in the Member State*** where the generic is to be marketed. It is sufficient for the innovator product to be or to have been authorised in one Member State in order to serve as a reference product for further marketing authorisation applications in other Member States, where the product is not or has not been licensed. Yet, there is no explicit supervision or sanction in Review 2005 for a situation where the respective Member State would not provide the requested information in compliance with Directive 2001/83/EC, Article 10, e.g. the full composition of the MP in question, on time or when the same MS provides it in the national language. Thus, measures for a successful implementation of the respective provisions are still not optimal. The documentation requested must be relevant for the assessment of the submitted generic medicinal product. (30,31)

In 2006, a CMD(h) guidance on the European Reference Medicinal Product has been issued, which is complementary to the NTA, Chapter 1, Revision 3. The information given in this document is of first importance for the Decentralised Procedure (DCP) as the Mutual Recognition Procedure (MRP) is based on an already authorised medicinal product in the RMS and therefore all arising problems with the ERP in the RMS will already have been solved during the national marketing authorisation process and should be addressed in the Assessment Report (AR) of the RMS. CMD(h) has agreed on the necessary minimum of information to be provided by the competent authority of the MS where the information on the ERP is available or has been authorised, to the competent authority of the MS where the MA application is submitted. This minimum information is defined in the respective CMD (h) guidance which provides that the RMS will act on behalf of the CMSs in order to facilitate the process for all CMSs where the reference medicinal product has not been authorised. It will also be an integral part of the Preliminary Assessment Report (PrAR) to be prepared by the RMS. (28)

2.1.4 Definition and requirements for a biotechnological medicinal product

The different approach for the authorisation of “generic” products to **biotechnological medicinal products**, i.e. biosimilar products, is already reflected in the Annex to the Human Medicines Code 2001/83/EC, which was amended in 2003 and became Directive 2003/63/EC. This Directive remains applicable to Directive 27/2004/EC, Article 10. (6) (13,31)

The general requirements for generic products are not sufficient for biosimilar products because any changes in the manufacturing process may generate significant differences in terms of quality, safety, and efficacy. The efficacy and safety of a biosimilar biotech molecule is not necessarily to be the same for all indications. Therefore, according to the pharmaceutical Review 2005, the applicants for biosimilar products will have to provide to EMEA specific preclinical and clinical data for each therapeutic indication and also for new routes of administration. (31)

The extent and the nature of non-clinical tests and clinical studies on biosimilar products are determined on a case-by-case basis in consideration of various factors. According to Review 2005, many guidelines specifying the "appropriate pre-clinical tests or clinical trials" clarifying the general requirements for biological products in terms of safety and efficacy are issued or are under preparation. Nonetheless, there are still many questions about the data required to demonstrate biosimilarity with a biological reference product and how companies will manage after having received scientific advice by EMEA and additional guidelines are available. (32,33,34)

Both the precise definition and the requirements for this therapeutic category in Article 10 (6) of Directive 2001/83/EC, as amended, have created a number of implications. The process for marketing authorisation and preparation of biosimilar medicinal products is clearer and more precise than in the past, where even in case of a positive opinion of CHMP like INN Somatropin – trade name Omnitrop (London, 26 June 2003, CPMP/3184/03) - no marketing authorisation on Somatropin (Omnitrop) was granted by the Commission as Omnitrop was not considered to have well-established use and thus was not authorised till the Directive 2004/27/EC had come into force. Omnitrop was authorised later like a first biosimilar product authorised by the Community after Review 2005 was introduced and the Directive was already in place. (35,36,37)

2.1.5. Prolongation of the "data exclusivity period" - The new EU harmonised legal framework

The EU pharmaceutical legislation, pursuant to the Directive 2004/27/EC, Article 10.1, and Regulation 726/2004, Article 14. (11), creates a harmonised EU eight-year data exclusivity provision with an additional two-year marketing protection provision.

This effective **10-year marketing protection** can be extended by an additional **one-year maximum** if, during the first eight years of those ten years, the marketing authorisation holder (MAH) obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior

to their authorisation, are deemed to bring a significant clinical benefit in comparison with the existing therapies.

This so-called 8+2 (+1) formula applies to new chemical entities (NCEs) in all procedures and to all Member States (unless certain Member States, who joined the EU in 2004, are awarded derogations, which they can request following the publication of the new law - see Figure 1). In practical terms this means that a generic application for marketing authorisation can be submitted after Year 8 without providing results of pre-clinical tests or clinical trials based on the prerequisite that it can be demonstrated that the medicinal product is a **generic of a reference medicinal product** which has been authorised under Directive 2001/83/EC, Article 6, for not less than eight years in any MS or the Community. (13,31)

This is also possible now for the Centralised Procedure, where before 20 November 2005 the data exclusivity period was 10 years. Practically, that means that the data exclusivity period will fall for generics will be reduced from 10 years to 8 years for all reference products approved centrally, as well as for products authorised by national or mutual recognition procedure in the eight MSs, i.e. Belgium, Germany, Luxemburg, France, Italy, the Netherlands, Sweden, and the UK, where the data protection period was 10 years.

The introduction of an identical, harmonised data protection period (8 years) in all Member States and for all procedures will facilitate the availability of generic medicinal products in all MS and constitutes a compromise between the former 6-year countries, i.e. Austria, Denmark, Finland, Spain, Ireland, Portugal, Greece and all new EU MS and the former 10-year countries (see Table 2). (38)

2.3. Transitional law for data exclusivity

Under the transitional provision in Article 2 of Directive 2001/83/EC "dead-lines for the transposition of the amending Directive", an extra transitional period is provided for in respect of the introduction of the amended protection of data exclusivity period.

The previous period of data exclusivity is valid for all MP-dossiers submitted before 30 October 2005. In consequence, the results of the change will only be discernible for all six year MSs data exclusivity from that date, especially for those MS that have joined the EU in 2004, in which the data exclusivity period will then increase dramatically from no data protection at all to 6 years to the new period of 10 years. If the extension to 10 years would have been operational immediately, this could have lead to serious undesirable consequences on the affordability of the medicinal products to some of these markets.

The new periods of the exclusivity provision will be applied to reference medicinal products whose marketing authorisation applications are submitted after the new provision has come into force (October 2005). Thus, in reality the generic industry will profit from the "eight-year provision" for the centrally authorised MP not earlier than 2013. (31)

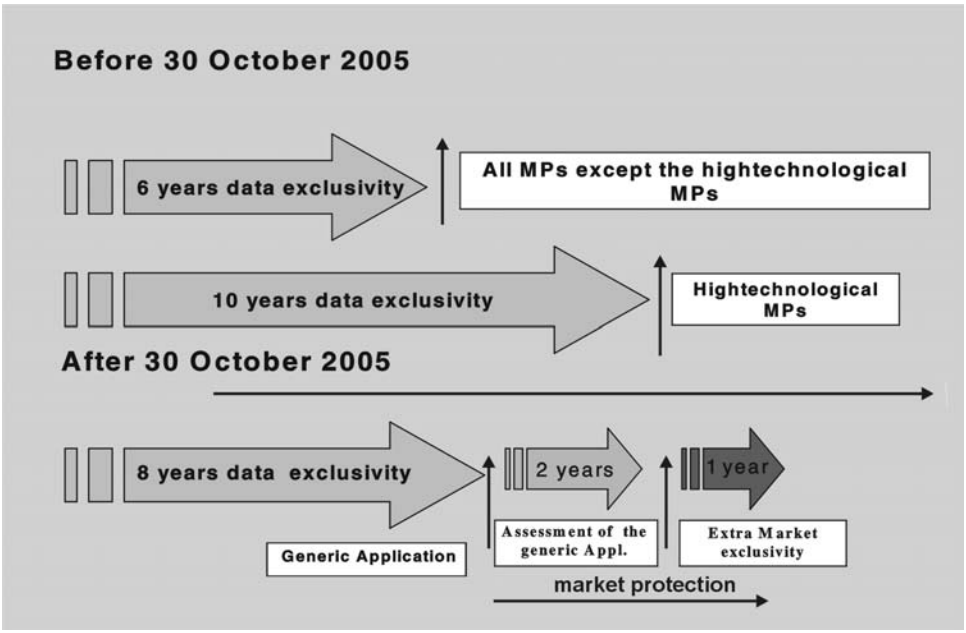

Figure1. Harmonisation of the data exclusivity process in EU MSs acc. Regulation (EC) 726/2004 and Directive 2004/27/EC

2.4. Additional protection for new therapeutic indications

The Commission is also in favour of harmonisation of the time periods and the linkage between data protection for nationally authorised medicines and corresponding patent protection. Incentives are provided to further improving existing medicinal products, in particular to develop new and important therapeutic indications. Such an incentive is an additional data protection period.

With reference to the additional one-year protection for new therapeutic indications, Directive 2001/83/EC, Article 10. (1) and Regulation (EC) No 726/2004), Article 14 (11) are giving incentives to those medicinal products which **"bring significant clinical benefit in comparison to the existing therapies".** Actually, that additional year of data exclusivity could be applicable mainly to products which "constitute significant, therapeutic, scientific innovation" ((Article 3, (2) (a), Regulation (EC) No 726/2004)), which could constitute such clinical benefit. (23)

The introduced Article 10 (5) of Directive 2001/83/EC as amended also allows an additional year of data exclusivity for MP with well-established use (Part II of the Annex to Directive 2001/83/EC as amended by Directive 2003/63/EC). A new indication authorised under the new provisions of Directive 2004/27/EC amending Directive 2001/83/EC and of Regulation (EC) No 726/2004 may benefit from an additional year of protection. A draft guideline on "elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11 years) marketing protection period" (EMEA/CHMP/63980/2005) is already available. The novelty of the indication for a MP and the claim for significant clinical benefit in comparison with the existing therapies will be evaluated by CHMP or national Competent Authorities on a case-by-case basis. The "new therapeutic indication" means a new target disease for the MP and/or change from treatment to prevention or diagnosis of a disease. (31,39)

A draft guideline on new therapeutic indications for well established substances is being elaborated since the end of 2005. To promote research on old substances, paragraph 5 of Article 10 of Directive 2001/83/EC, as amended by Directive 2004/27/EC, states that where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted.

Significant pre-clinical or clinical studies have to be carried out in relation to the new indication. This one-year protection would apply to authorisations for new indications for MP with well established use granted after 30 October 2005. The Draft-Guideline in conjunction with Chapter 1 of Notice to Applicants describes "new therapeutic indication" and "significant preclinical or clinical studies" and outlines the principles and procedure to claim one-year data exclusivity period. (23)

Significant clinical benefit - in comparison with existing therapies – is summarised in the said guideline, which is based on greater efficacy and safety in comparison with the existing therapies. An additional Type II variation or Annex II extension of the Regulations 2003/1084/EC and 2003/1085/EC is also possible to be applied for such new indication and the current International Classification of Diseases 10 (ICD 10) should be used as a basis for diseases' classification. Examples which are not considered to provide significant clinical benefit are presented in the same draft guidelines from December 2005. It is recommended that MAH request scientific advice from competent authorities to assess the safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies. (39,40,41,42)

2.5. Additional protection for new data supporting a change of classification

A change of classification authorised after the rules in Review 2005, Directive 2004/27/EC and amending Directive 2001/83/EC and of Regulation (EC) No 726/2004 started to be applied. The 1 year period of protection covers significant pre-clinical and clinical trials conducted for the purpose of a change of application. The competent authorities must assess whether the change is based on significant preclinical and clinical tests according to Article 74a of Directive 2001/83/EC as amended. (31)

2.6. The "Bolar" Provision

The Review 2005 introduced the so called "Bolar" provision in the Community, which relates to patent law and allows the generic industry to carry out development of a generic medicinal product while the patent of the reference product is still in force. Finally, to counterbalance the practical impact of the extension of the data protection in certain MS, Article 10 (6) in Directive 2004/83/EC directs the generic industry to undertake the necessary studies and trials and even to apply for marketing authorisation within the patent term without this being contrary to patent right. The new legislation concerning the "Bolar" provision provides the opportunity of undertaking commercial development activities such as conducting clinical trials in the EU for the generic industry, while the reference product is completely protected by a patent. (31, 43, 44)

2.7. Single data base of Reference medicinal products in the EU

To date, no single data base on reference medicinal products in the EU exists. The Community register provides information only for the centrally authorised medicinal products, however, for all reference medicinal products authorised at MS level there is no single official data base. In contrast, the US Food and Drug Administration (FDA) has an official website providing information on reference products, the so-called "Orange Book". (45)

A serious challenge for the process of submitting a generic application is the absence of an official EU Data Base of all reference medicinal products as this kind of information is only available for products authorised under the Centralised Procedure and consequently published in the Community Register of medicinal products and on the website of EMEA (Article 13 (3) of Council Regulation (EC) 726/2004). (36,45a,46)

The European Public Assessment Report (EPAR) applicable to centrally authorised products is a concise document which highlights the main parts of the CHMP scientific discussion leading to the CHMP opinion and provides an

extract of the scientific information. The content of the EPAR is derived from the reports produced during the assessment of the documentation submitted by the applicant together with the scientific discussion at CHMP level.

The legal basis for its creation and availability was set out in Article 12 (4) of Council Regulation (EEC) 2309/93 with the creation of the Community Authorisations. Regulation 726/2004, Article 13, obliges the EMEA to publish the EPAR immediately. Obviously, the aim is public transparency, whereas the pharmaceutical parties could benefit from the information provided for different purposes, e.g. for the development of further generics. (10, 11)

For non-centrally authorised products, the generic applicant can use different ways for collecting information like SmPCs and ARs from the various homepages of the competent authorities in the EU or from databases where the access to the authorised medicinal products is permitted only against payment. To date, the main problem is that only 1/3 of all 27 MSs have accessible homepages is English and even the wording in the different MSs for the term "Generic product" is still divisive.

On the website of the Heads of Medicines Agencies (HMA) a new data base has been established for those medicinal products involved in the MRP/DCP procedures. The former MRFG has developed this Mutual Recognition Index (Product Index) which contains the products approved via MRP/DCP. The system is accessible on this website of the EU regulatory bodies. The mutual recognition procedure and the decentralised procedure have grown significantly over the years, and this process is shown in the reports and the statistics on the website of the HMA so called Mutual Recognition Index (MRI).

Nevertheless, the absence of a single EU source regarding the information on the RPs authorised under national or MRP procedures, and the information provided only in national language by any regulatory authorities may pose a serious challenge for the generic industry to getting the relevant information, especially in those situations where the RP has no identical authorised SmPC in the different MS.(30)

Table 2. Data protection period of the reference product according to Directive 2001/83/EC, Regulation (EC) No 2309/93 and Directive 2004/27/EC, Regulation (EC) No 726/2004

Issue	**Before end 2005 Data exclusivity Directive 2001/83/EC Regulation (EC) 2309/93**	**After end 2005 Data exclusivity Directive 2004/27/EC – 31 Oct= Regulation (EC) 726/27/EC -20 Nov.**
Data exclusivity by CP Procedure	10 years for MP submitted through CP till 20 November 2005	MP submitted through CP after 8 years are elapsed of the initial authorisation of the original product 8+2 (+ 1) year for new indication, submitted in the first 8 years
Market exclusivity	10 years + period of first MA for similar MP for MP submitted through CP (EEC) 2309/93 (till 20 November 2005)	MP submitted through CP (EC) 726/2004 after 20 November 2005 or 10 years+1 year(for new indication)
Data exclusivity Ex-concentration procedure	10 years for MP authorised following CPMP opinion Article4 87/22/EEC	10 years for MP authorised following CPMP opinion Article 4 87/22/EEC
MS with 10 years Data exclusivity Period	Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Sweden, and the UK. (Single decision procedure of MS)	Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Sweden UK. **In Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway, and Iceland and the 10 new Member States**
6 years Data exclusivity Period	Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway, and Iceland and the 12 new Member States incl. Bulgaria and Romania (Single decision procedure of MS)	**6 years data exclusivity only allowed in the Transitional period till 2013 Directive 2001/83/EC as amended Article 2 in Dead-lines for the transposition**
Definition of reference medicinal product (RP)	**No legal definition exist**	**Legal definition** in Directive 2004/27/EC, Article 10.2a
Bioequivalence between GP and RP	**Unclear legislative issue, one of the conditions for essential similarity acc. Directive 2003/63/EC**	**Clear legislative issue** Directive 2004/27/EC, Article 10.2 (b)
Authorisation of GP applied to biosimilar products	**No explicit legal basis**	**Legal definition of Biosimilar product** Directive 2004/27/EC, Article 10.6
Definition of generic medicinal product	**No legal definition exist**	**Yes** Legal definition is in Directive 2004/27/EC Article 10.2b
Additional protection for a new indication	**No legal issue exist**	Additional protection for new indication Directive 2004/27/EC Article 10.1
Line Extension (LE) protected by a separate exclusivity period	**Unclear legislative provision for LE** ECJ 29 April 2004 (Novartis, C-106/01) NTA stated that the data exclusivity is not related to the dosage form, strength and schedule	**Clear legislative provision for LE No additional data exclusivity for LE**, Article 6, 2001/83/EC, which is part of the same global marketing authorisation dossier as the initial MP

3. EU Marketing authorisation procedures of MPs in terms of accelerated market access

3.1. Legal issue of Community Authorisation

3.1.1. Development of the centralised procedure in the European Community

Since the implementation of Council Directive 65/65/EEC, medicinal products can only be placed on the market in the European Union once they have received a marketing authorisation.

With Article 11-13, Directive 75/319, a Committee for evaluation of particular pharmaceutical medicinal products - Committee for Proprietary Medicinal Products (CPMP) - was established. Nowadays, the Committee is named the Committee for Medicinal Products for Human Use (CHMP). This Committee gives an opinion whether a particular medicinal product filed via the centralised procedure complies with the EU requirements.

The marketing authorisation of proprietary medicinal product under the centralised procedure started with the second Council Directive 75/319/EEC and the procedure and the scope for the centralised marketing authorisation evolved gradually from 1965 to 2005 (see Table 1). (9, 10,11,14)

Regulation (EEC) 2309/93 of the Council was approved on 22nd July 1993 and it established an Agency for the evaluation of medicinal products (EMEA) in 1995. In addition, it laid down Community procedures for authorisation and supervision of medicinal products for human and veterinary use for all Member States. A network of EMEA, national competent authorities, and the European Commission works together in order to provide scientific evaluation and decision on a marketing authorisation application in this procedure. Once a product has been granted a Community marketing authorisation, any post authorisation regulatory activities, e.g. variations, renewals, must equally be done via the centralised procedure. (10)

After six years of experience with the Community procedure introduced in 1995, the general opinion within all interested parties and the Commission as stated in the 2001 report was that the centralised system had worked with a high level of satisfaction and the procedure had proven its effectiveness for biotechnology and innovative medicinal products. There was a general recognition of the very considerable contribution made by the EMEA. Nevertheless, the Commission considered that in order to motivate competitiveness by helping innovative companies and to cope with foreseeable future evolution in terms of innovation and technical progress, the scientific profile of the EMEA should be reinforced. The development of new technologies had also required a review of the assessment procedures where solutions had been needed in situations not yet

covered by the existing medicinal legislation till 2004. (16,17)

The objectives set by the Commission Report in 2001 resulted in many new legislative amendments in the centralised procedure that were implemented with Council Regulation 726/2004, replacing Regulation (EEC) 2309/93 and in the decentralised way of authorisation, mainly Directives 2004/27/EC and 2004/24/EC. The new Directives introduced a number of amendments to the existing Community Codes on human and veterinary medicines (Directives 2001/83/EC and 2001/82/EC) relating to the scope and to the accelerated authorisation procedure presented in detail in NtA, Volume 2AChapter 4, last revision in 2006. (38,47)

As a consequence of the revised EU pharmaceutical legislation, the name of the EMEA was changed from "European Agency for the Evaluation of Medicinal Products" to the "European Medicines Agency" (EMA), nevertheless the acronym "EMEA" remained unchanged. (11)

The medicinal Community Procedure leads to a single marketing authorisation valid throughout the whole enlarged EU which is granted in the form of a Commission decision and is based on a scientific evaluation by the Committees established within the EMEA in London. The Community marketing authorisation confers the same rights and obligations in each Community country as a marketing authorisation granted by a Member State.

For human medicinal products, the scientific evaluation of applications is undertaken within 210 days by the CHMP. The CHMP has one representative and an alternate per EU MS.

In addition, the new legislation gives the CHMP the possibility of appointing up to five co-opted members to provide additional expertise in particular scientific areas. For the first term after coming into force of the new Regulation, the CHMP elected five co-opted members who joined in September 2004. Further more, each of the European Economic Area (EEA) with folloing countries - Iceland, Liechtenstein and Norway, may nominate a member and an alternate who contribute to the work of the CHMP but are not eligible to vote in decisions of the CHMP. The Committee - through the respective Rapporteur and Co-rapporteur - contracts out assessment work to experts in the Member States. An additional Committee for Herbal Medicinal Product (HMPC) for evaluation of monographs and products was set up pursuant to Regulation (EC) 726/2004.

Scientific advisory groups may be established to provide advice to the Committee in connection with the evaluation or specific types of MP or treatments. During the assessment process of an application, the Rapporteur together with the Co-rapporteur prepares an assessment report which forms the foundation for the CHMP opinion. In the process of evaluation the clock may be stopped while the applicant responds to the request for supplementary information (RSI) and to allow time for the applicant to prepare for an oral explanation, if required. At the conclu-

sion of the scientific evaluation, the CHMP opinion is transmitted to the European Commission to be transformed into a single Community marketing authorisation applying throughout the EEA or a rejection of the application. (11,48,49)

Centralised marketing authorisation procedures of MPs in the EU Regulation (EC) 726/2004

Important new features were introduced in 2005 including an expansion of the scope of the procedure, a shortening of the timelines for the Commission decision, and the establishment of new specific marketing authorisation procedures, like:

Accelerated marketing authorisation procedures according to the Regulation 726/2004

- **Conditional Marketing Authorisation**, Article 14 (7) of Regulation 726/2004 and the published regulation clarify the obligation in that process,
- **Marketing Authorisation under exceptional circumstances**, pursuant to Article 14 (8),
- **Accelerated centralised procedure**, based on Article 14. (9) (Figure. 2)

Compassionate Use, Article 83 (2) of Regulation 726/2004 is directed to medicinal products which are not authorised yet in Europe and may be given to patients in a clinical trials. These products should be either under investigation in clinical trials or subject to review by autority. (23)

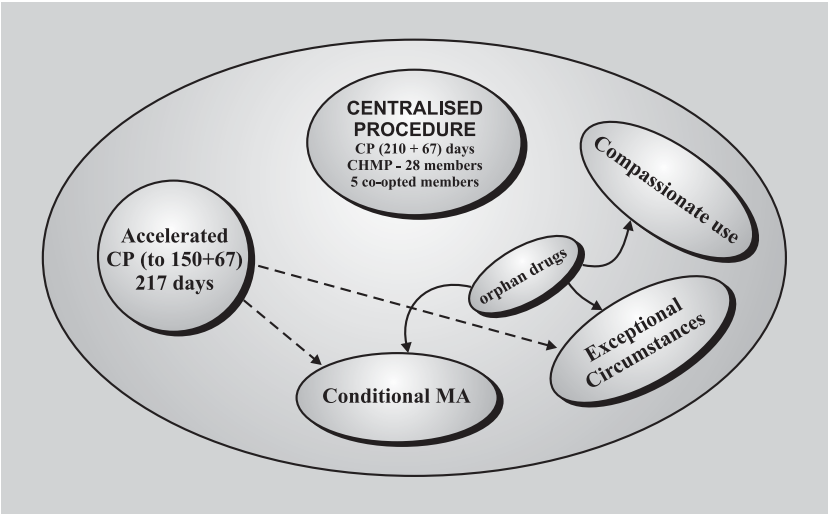

Figure 2. Centralised marketing authorisation procedures of MP, pursuant to the EU Regulation (EC) 726/2004

3.1.2. Extending the scope of the Centralised Procedure

According to Regulation (EEC) 2309/93 the CP was mandatory for certain medicinal products developed by means of biotechnological processes and it was optional for certain other categories of medicinal products such as those containing new active substances and those presented for an entirely new indication constituting a significant innovation (Part A and B of Annex I of the same regulation).

The number of human medicinal products that have to be authorised at Community level has been broadly extended in the scope of Council Regulation 726/2004, Article 3 (1) (2) and in the Annex of the same Regulation, where new active substances in the therapeutic indications acquired immune deficiency syndrome, cancer, neurodegenerative disorders, and diabetes have been included as falling under the mandatory scope of the CP since 20 November 2005. (11,23,50)

In addition, four years after the date of entry into force of Regulation (EC) 726/2004/EC, after May 2008, all medicinal products containing new active substances in the therapeutic indications of autoimmune diseases and other immune dysfunction or viral diseases will fall within the mandatory scope of the CP. The Commission has also established a new regulatory framework to cover certain new or future forms of medical treatment, in particular these related to gene therapy and cell therapy and to provide for an optimal balance between innovative medicinal products and generic medicines (see Table 3 and Figure 3). In the EMEA draft guideline in accordance with article 3 (2) (b) of Regulation (EC) No 726/2004. 21/12/0 the procedure for confirmation of the eligibility to the CP and the criteria for new active substances not authorised in the Community are presented. (11,23,52)

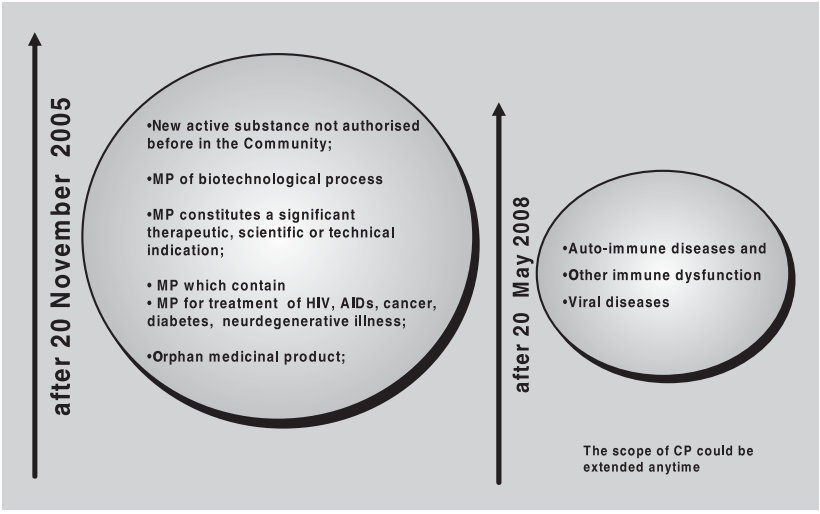

Figure 3. Medicinal products under CP in the Review 2005, Art. 3 (2) and Annex of Regulation (EC) 726/2004.

In the period 1995 - 2004 the CP proved its effectiveness in assessing medicinal products derived from biotechnology and other new technologies. An important reform in the new legislative framework was the extension of the scope of the CP to all new active medicinal substances in the mentioned indications to go through the CP.

Table 3. Comparison between the Centralised Procedure in Regulation (EEC) 2309/93 and in Council Regulation (EC) 726/2004

TOPIC	Centralised Procedure/ Regulation (EEC) 2309/93 (before 20 November 2005)	Centralised Procedure Council Regulation 726/2004 (since 20 November 2005)	Advantages for the Council Regulation (EC) 726/2004 which modify Regulation (EEC) 2309/93
Centralised procedure (CP)	Normal CP	Centralised Procedure Accelerated CPs	**New Accelerated CPs**
Temporary MA within the CP	1. Exceptional Circumstances	1. MA under Exceptional Circumstances **2. Conditional Authorisation** **3. Compassionate use**	Two new temporary procedures within the Centralised Procedure were introduced **2. Conditional Authorisation** **3. Compassionate use**
Name of the MP	Single Name in the EU	Single **Invented** Name in the EU	**Single name in the EU left**
Scope of the Centralised Procedure (CP)	**- Annex I** **Part A-**biotechnological MP - recombinant DNA technology - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes-transformed mammalian cells **- Part B - not obligatory for the CP**	- New active substance (NAS) - innovative MP - Immunological. MP for the treatment of animal diseases that are subject of prophylactic measures - MPs in the Annex - Reg. (EC) No 726/2004	Generic products, where the originator is initially authorised, could use the option of CP or DP **- biosimilar only via CP** **- orphan MP only via CP**
Type of Applications	**full dossier acc. 2003/63/EC (stand alone application)** - bibliographic application. - mixed application **abridged application.** - informed Consent App. **- essentially similar to RP via CP**	**full dossier 2003/63/EC (stand alone application)** - bibliographic application - mixed application **abridged application** - informed consent application **- generic application bioequivalent to RP**	- provision for MA of generic product where the reference product has undergone CP - provision for biosimilar - after 8 years of the MA of RP generic application possible
Assessment	CHMP, CVMP, COMP Working Parties	CHMP, CVMP, COMP,HMPC, PDCO**, CMD (h) +** 12 EMEA -Working Parties 7-Scientific advisory groups-(SAGs) 3 Other CHMP-associated groups 3 Temp. Working Parties	New Committees and Groups HMPC PDCO CMD (h)
CHMP Opinion SmPC, PIL	Art. after 210 days	Art 6 (3) After 210 days **Art 14 After 150 days**	**Accelerated assessment in 150 days (60 days shorter the standard CP)**
CHMP send Positive Opinion SmPC, PIL	**+30 days (total 240 days)**	**+15 days (CP-225 days) Acc. Assessment - 165 days)**	**15 days shorter**
Commission Draft Decision	**+ 30 days (total 270)**	**+15 days Art. (10) (CP- total 240 days) (Accelerated Assessment CP- 180 days)**	**15 days shorter**
Member State Draft Decision	**+28 days (total 298 days)**	**+22 days (CP - total 262 days) (Acc. Assessment - 202 days)**	**6 days shorter**
Commission Decision	**No period fixed (over 300 days)**	**+15 days (standard CP - total 277 days) (Accelerated CP. - 217 days)**	**New CP 36 days shorter (Acc. Assessment 60 (29%) days shorter**

3.1.3. Duration of the Centralised Procedure

With the Review 2005, the legislative period for assessment of MP at the Committee level remained unchanged, only the timelines for the subsequent Commission decision were significantly reduced. Till the draft Community Decision, the time is decreased by 36 days (12%) (see Table 3, Figure 4), shortening the entire period of time to a Community authorisation to be no longer than 277 days (for comparison, according to the previous legislation the procedure could take up to over 300 days).

For instance, a MS will now have 22 days to forward its written observation on the Commission Draft Decision (CDD) instead of 28 days ((Article 34 (2) of Directive 2001/83/EC)). In (EEC) Regulation 2309/93 the period for the CDD according to Article 10 (3) was not fixed and now all changes in terms of shortening the marketing authorisation time are focused at Commission and Standing Committee level, where obviously more expert capacity should be involved than before November 2005 in order to follow operatively and strictly all new legislative steps. (10,11)

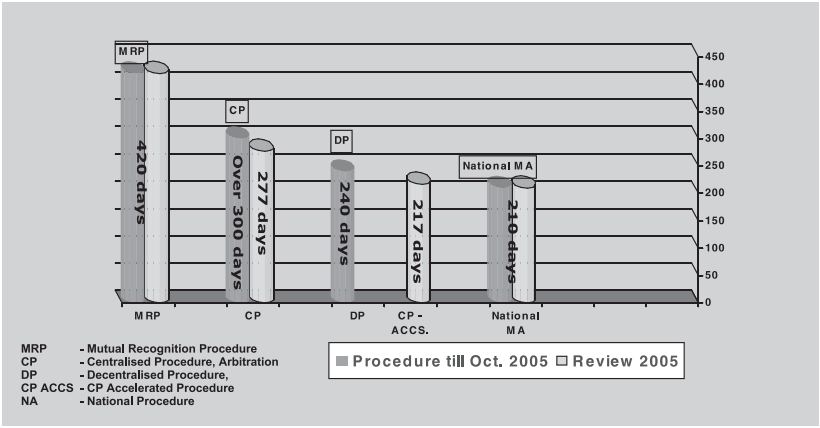

Figure 4. Descending presentation of the duration of the different MA procedures of MPs in the EU as defined in the legislation (without clock stop).

In 2001, EMEA had introduced instruction CPMP/495/96/ of 18 September 2001 on the accelerated evaluation of products indicated for serious diseases. The standard time frame of 210 days was applied with shortening the time for preparing the internal Rapporteur and Co-Rapporteur's Assessment Report (so called "70 days AR"). With the review, the procedure for accelerated assessment has been legally defined. (11,52)

The updated legislative pharmaceutical documents regarding the Centralised Procedure after end 2005 introduced an accelerated assessment

period (217 days), which is by 60 days (22%) shorter than the standard, current CP (27 days). Where the MP is linked to a public health issue and represents an "appreciable therapeutic innovation", the time for assessment should be reduced from 210 to 150 days. According to Article 14 (9) of Regulation (EC) 726/2004 the applicant can request an **Accelerated Procedure** to be applied. A legal provision has been introduced under the Regulation for the applicant to formally request an accelerated evaluation. For such assessment with which the procedure is 60 days (22%) shorter than the standard procedure in the CP, serious responsibilities should be taken into consideration by EMEA staff and the CHMP members to ensure that the opinion is provided within in the shortened time frame (Day 80 Rap assessment report). (11)

In total, the accelerated evaluation of CHMP and the Commission decision should be finished within 217 days (see Table 3). A guideline of EMEA on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004 (EMEA/419127/05) with final implementation in July 2006, presents all details and new steps for the accelerated approval at the Community level. Requests for an accelerated assessment should be submitted 4-6 months in advance with the provision in the EMEA guidance on practical considerations relating to the legislation for the Centralised Procedure (see NtA, Volume 2, chapter 4.3). (23, 38,53)

In the previous legislation (before 20 November 2005) such shorter scientific assessment procedure was not legally possible. Due to this guidance, with two Revisions from 2006, the procedure now is already directed to faster authorisation of some innovative products in the pharmaceutical field. In order to make medicinal products available for patients as quickly as possible, the opportunity of a speedier Committee evaluation is highly recommendable. Actually, the total procedure with all steps at the Community level should not be longer than 217 days posing a great challenge not only for the regulatory authorities but for the industry as well. For the first time such shorter review times with 60 days of the assessment than the standard CP in the previous legislation is set up legally requiring enactment of new timetables to comply with the new regulation. (53)

3.1.4. Management and exchange of medicinal product information

After the accession of Romania and Bulgaria to the EU, there are now 23 languages involved in the CP. Creating and managing the very large number of documents (usually between 600 and 1000 documents for a single trade name) in paper or as an electronic file brings a very significant burden to Member State competent authorities and EMEA. One potential solution to this issue is to develop a system for management and exchange of medicinal product information, the so called Product Information Management (PIM).

PIM has been introduced by the EMEA for the first time in November 2005. The main idea is to increase the efficiency of the management and exchange of product information (SmPC, PIL) by all parties involved in the evaluation process through the structuring of the information and its exchange by electronic means and improving the quality and consistency of the published product information. In order to support the regulatory review of product information produced using the PIM standard, a system (PIM Review System - PRS) has been developed for use by EMEA and by the Member State competent authorities. The details of the processes are defined in the EMEA - draft guidance (EMEA/413933/2005). (54)

PIM may be used either within, or outside, the CTD and the documents and data applied to product information in all languages for the CP are to be initially introduced for this procedure. By PIM submission, there will be no need to process the product information documents as paper or Word documents. On the basis of the electronic PIM information the validation and review will be done and the product information will be automatically generated by the PIM system from the underlying information.

The PIM standard depends upon having an agreed definition of the content and layout of the product information documents. In support of the Centralised Procedure it has been possible to define the standard based on the Quality Review Documents (QRD) templates.

For Mutual Recognition and National Procedures, before the end of 2005 these standards were not consistent with the QRD templates and furthermore there are several areas where national standards apply, notably with the package leaflet. When the use of PIM is implemented within the CP the standard may potentially be further developed to support products in the Mutual Recognition/Decentralised and National Procedures. The CMD already proposed the adoption of the QRD templates in MRP/DCP and is also proposing the adoption of PIM.

The implementation of Article 10 (1) of Regulation 726/2004, which foresees a reduction to 15 days of the period allowed from opinion to the submission of opinion documents to the European Commission will increase this burden. Use of PIM in the CP greatly eased these challenges through management of the underlying information and re-use of repeated information rather than a focus on the very document. (54)

3.1.5. New regulatory issues for orphan medicinal products

Over 8000 different rare disorders have been identified worldwide. In the EU, with great variety of population groups, 27-36 million patients have rare diseases, while in the US 10 to 20 million patients are affected.

Rare diseases are life-threatening or chronically debilitating conditions

affecting in the range five in 10,000 people in the European Union, which according to the last statistics corresponds to 246,000 persons in the 27 EU Member States. (July 2007). Most of the people represented by these statistics suffer from even less frequently occurring diseases affecting one in 100,000 people or fewer. Medical and scientific knowledge about rare diseases is lacking. Less than 1,000 diseases – essentially those that occur more frequently – benefit from a minimum of scientific knowledge. Therefore, the European Union's Seventh Framework Programme for Research and Technological Development (FP7, 2007 - 2013) is intended to invest into research into rare diseases and will also include development of human phenotypes.

The European Union orphan medicines legislation was introduced in 2000 and provides a number of incentives for the development of medicines for rare diseases. The designation procedure identifies 'orphan' eligibility for such incentives, which include 10-year market exclusivity in the designated indication after MA. More than 50% of the designations granted to 2002 were for rare diseases in oncology and more than 65% of the designations are for diseases in children. (55, 56)

Implementation of EU orphan drug legislation was timely to address the unmet medical needs of patients suffering from rare diseases within the Community as they deserve access to the same quality of treatments as other patients. The orphan legislative procedures are part of a broader Community pharmaceutical policy to identify rare diseases as a priority area for action in the field of public health. Regulation (EC) 141/2000 of 16 December 1999 lays down a community procedure for the designation of a medicinal product as an orphan medicinal product and the criteria for designation. EU orphan legislation entered into force in April 2000. The Committee for Orphan Medicinal Products (COMP) has been established within EMEA in March 2000 and has played an important role in stimulating the development of orphan medicinal products (OMP) and in implementing the legislation. (57)

A report reflects upon an account of the more than 5 years of experience gained as a result of the application of this legislation and summarises public health benefits, which have been obtained through orphan legislation. It has been published as a contribution to support the European Commission in finalising its general report before 22 January 2006.

With the Annex of the new Regulation (EC) 726/2004, the CP is now mandatory for all marketing authorisation applications relating to designated orphan medicinal products. Between April 2000 and April 2006, 718 applications for orphan designation were submitted to EMEA and 342 (47%) out of them received a marketing authorisation as orphan drug. Only for the last consecutive three years from 2004 to 2006, altogether 330 orphan applications were submitted and COMP adopted 244 (74%) positive opinions of all desig-

nated orphan drugs. In the year 2006, the submitted products related to rare diseases were 104 and the positive Commission decisions were 80 (77%). The year 2000, when the orphan decisions granted by the Commission, were only 14 (11%) of all 72 submitted orphan applications, proves the significant increase in research and placing on the market of orphan products in the EU. (58,59)

EMEA and its Committee on Orphan Medicinal Products (COMP) have taken on an important role in stimulating the development of orphan medicinal products and in implementing the legislation. The COMP, together with the Commission and in consultation with stakeholders and interested parties, has developed appropriate guidance to establish a sound EU process to designate orphan medicinal products eligible for the incentives as provided by the legislation. For the purpose of designation and to support the rationale for development of the product in the same proposed condition some preliminary preclinical and/or clinical data are required. A pharmacological concept, not supported by any form of evidence or result, would generally not be considered as sufficient justification by the COMP. (59, 60)

The therapeutic indication granted under the terms of a marketing authorisation must fall within the scope of the designated orphan condition. According to Article 7 (3) of Regulation (EC) 141/2000 the marketing authorisation granted for an orphan medicinal product shall cover only **those therapeutic indications** which fulfil the criteria set out in Article 3, where the orphan designation is established (57):

- life-threatening or debilitating nature of condition;
- medical plausibility of the proposed orphan indication;
- prevalence of the condition in the Community is not more than five in 10,000 or it is unlikely that the marketing of the medicinal product in the Community, without incentives, would generate sufficient return to justify the necessary investment;
- no satisfactory method of diagnosis, prevention, or treatment exits or if such a method exits the medicinal product will ensure significant benefit to those affected by the condition.

For diseases with a prevalence of more than 5:10,000 and the condition being not of a life-threatening or debilitating nature or not meeting the other requirement for orphan designation, orphan designation can not apply. When for the same disease (condition) an indication with a sub-population could be established which could meet all above mentioned criteria for designation in Regulation (EC) 141/2000, the sponsor may develop the same product. “Orphan indication” is the proposed indication for the purpose of orphan designation. (57)

A request for designation may be made for an already authorised medicinal product if the designation request concerns a new orphan indication which is

not currently authorised and which complies with the requirements for orphan drugs. The marketing authorisation holder would be required to apply for separate marketing authorisation for the orphan indication. Orphan and non-orphan indications may not be covered by the same marketing authorisation. (59)

The criteria are laid down in Article 3 of Regulation 141/2000. The sponsor must either meet the criteria relating to the prevalence of a condition in the Community or the criteria relating to the potential for return on investment (Article 3(1) (a). In addition, the sponsor must meet the criteria relating to existing methods of diagnosis, prevention, or treatment (Article 3(1) (b)). Where a MA in respect on OMP is granted under CP, a 10 year market exclusivity period is applied. This period may be reduced to six years, if at the end of the fifth year it is established that the orphan criteria pursuant Article 3 of Regulation 141/2000 are not longer met.

Regarding Article 3 of Regulation 141/2000, orphan designation may be granted for the same therapeutic indication to a similar medicinal product if the MAH of the original OMP:

- has given consent to the second applicant;
- is unable so supply sufficient quantities of OMP.

If a second MP, although similar to the OMP already authorised, is safer, or more effective or clinically superior, this MP could be authorised like as an orphan drug. (57)

The word “condition” is used (rather than disease) to ensure that the regulation applies also to treatments for conditions which are not classical diseases, in particular genetic disorders. The term “condition” is defined in the Guideline (ENTR/6283/00 with last Version of October 2006) on the format and content of applications for designation as orphan medicinal products as “any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)”. “Orphan condition” is the condition that meets the criteria defined in Art. 3 of Regulation 141/2000. “Orphan indication” is the proposed indication for the purpose of orphan designation. (60)

The marketing authorisation application must include a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria. This information will be assessed in parallel with the marketing authorisation application.

Till 20 of November 2005, orphan medicinal products were alternatively eligible for the CP or the MRP. After November 2005, according to Regulation (EC) 726/2004, Annex (1) only the CP is an option for orphan medicinal products, and it is not possible to opt for the Decentralised or Mutual Recognition Procedure for orphan medicinal products. (11)

Applicants may choose either to re-submit the Marketing Authorisation Application (MAA) from the ongoing National Procedure to the Centralised Procedure, or to withdraw the MAA. Both the re-submission to the CP and the withdrawal of MAA(s) from the ongoing national evaluation procedure were to be conducted in a transparent way and all parties involved informed accordingly. Ongoing evaluations of marketing authorisation applications for designated orphan medicinal products in National or Mutual Recognition Procedures were to be submitted to the CP after 20th November 2005, unless the applicant wished to remove the orphan medicinal product designation from the Community register. After submission of the dossier to the EMEA, the CHMP evaluation process proceeded according to the current Centralised procedure (NTA- 2A, Chapter 1 and EMEA/354611/2005). Orphan designated medicinal products, already approved via a National Procedure (NP) or Mutual Recognition Procedure (MRP) before 20 November 2005, are not allowed to continue to obtain further national marketing authorisations via a MRP or a "repeat-use" MRP. (23, 38, 47)

All incentive measures to aid the research, marketing, development and availability of orphan medicinal products is presented in the Commission guidance, where the regulatory incentives for orphan drugs and the legislative requirements of designated products in all MSs where presented except for Romania and Bulgaria, where no data are available. (61)

Companies with an orphan designation in accordance with Regulation of EC No 141/2000 for a medicinal product benefit from incentives products such as:

- protocol assistance (scientific advice during the product-development phase), based on Art. 6;
- 10-year market exclusivity based on Art. 8;
- financial incentives (fee reductions or exemptions), based on Art. 9;
- national incentives detailed in an inventory made available by the European Commission Art. 9.

Since 1 January 2007, orphan medicinal products are eligible for the following level of fee reductions: (EMEA 4042-01-Rev 7, from 18 December 2006)

- 100% reduction for protocol assistance and follow-up;
- 50% reduction for new applications for marketing authorisation;
- 100% reduction for pre-authorisation inspections;
- 50% reduction for post-authorisation activities, including annual fees (applies only to small and medium-sized enterprises in line with Regulation 726/2004 and Commission Regulation (EC) N 2049/2005), in the first year after granting of a marketing authorisation. (62,63)

3.2. Temporary Marketing Authorisations of medicinal products

3.2.1. Assessment for Compassionate Use of MPs

The European legislation requires that medicinal products falling under the mandatory scope of the CP are authorised by the European Commission before they are marketed in the Community. However, medicinal products that are not authorised yet in Europe, may be given to patients in clinical trials. In order to treat patients suffering from life threatening diseases, products that are not yet authorised in the EU may be provided to patients outside clinical trials under the legal provisions of compassionate use. These products should be either under investigation in clinical trials or subject to review by the EMEA for a marketing authorisation. The medicinal products concerned are only those aiming at treating a group of patients suffering from a life threatening disease, and who cannot be treated with a medicinal product already authorised in Europe. A legislative provision in Regulation (EC) 726/2004, Article 83, allows MP to be accessible to the patients as **"compassionate use"** before the MA is granted. The term "compassionate use" is directed to cover the supply of an unlicensed medicinal product to patients for whom no alternative medicinal products are available. The conditions for such exclusion are that the MP should be applied for authorisation under Article 6 of Directive 2001/83/EC or the clinical trials are ongoing. Compassionate use is usually reserved for the treatment of "chronically or serious and debilitating, life-threatening diseases". (11,31)

Pursuant to the same Article 83 (1) the Member States may make a medicinal product for human use belonging to the categories referred to in Article 3 (1) and (2) of this Regulation available for compassionate use. Guidance of EMEA and NTA, Volume 2a, Chapter 4, issue 3, are clarifying how the compassionate use could be applicable to the patient and group of patients in the different MSs. EMEA is responsible for keeping an up-to-date list of the opinions given for compassionate use on a public register available on the EMEA website (Product-Information Document). (36, 64)

Compassionate use programmes according to Regulation (EC) 726/2004, Article 83 (8), enable innovative drugs to be made available to the patients during the development programme. When a programme of compassionate use is set up, the applicant shall ensure that the patients taking part also have access to the new medicinal product during the period between the marketing authorisation and placing on the market. Directive 2001/83/EC, Article 5, allows MS to introduce national programmes to satisfy special patient needs in response to a "bona fide unsolicited order" formulated by an authorised health care professional and the product will be provided to an "individual patient". (11,31)

Compassionate use programmes are another option, which exists at the level of Member States, to make promising medicinal products available to patients much earlier than their placing on the market. Compassionate use programmes remain coordinated and implemented by the Member States.

The recommendations from the EMEA are complementary to the national legislations and are an option to the Member States that wish to use these recommendations for their patients, in order to facilitate the harmonisation of compassionate use programmes in Europe. The role of the EMEA and the role of the Member States regarding Compassionate use for centralised products is to provide recommendations to the Member States, on how to administer and use of the medicinal products for compassionate use, and identifying the patients that would benefit from the compassionate use programmes using such products. (31)

The conduct of compassionate use programmes remain the responsibility and the prerogative of the Member States The new legislation for "compassionate use" does not provide legislative recommendations defining the authorisation condition, which must be respected by the Member States. The guideline on compassionate use of medicinal product EMEA/27170/2007 from 17 of July 2006, pursuant to Art. 83 of Regulation (EC) No 726/2004, defines the scope and the general principles and "when the compassionate use is not applicable and discusses the compassionate use versus clinical trials and off-patient use. Compassionate use does not substitute clinical trials, nevertheless the safety data may be collected during that period and patients should be foreseen for inclusion in clinical trials before being offered a compassionate programme". (23,65)

The next step should be to extend EU legislation to cover individual import systems to supply patients with specific MP under clinical trials.

3.2.2. Assessment for Conditional Authorisation of MPs

A legal provision introduced under Article 14 (7) of Council Regulation 726/2004 permits a conditional licence, valid for one year, to be granted where there is a specific patient need. A Guideline, EMEA/509951/2006 and the Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council related to Article 14 (7) in accordance with the procedure laid down in Article 87 (2) will be covering Conditional Marketing Authorisation, which includes a MP for human use as defined in Articles 3(1) and 3(2) of the same Regulation (see Figure 5). (23,66,67)

The granting of a Conditional marketing authorisation will allow medicines to reach patients with unmet medical needs earlier than "normal" products falling under the scope of the CP and will ensure that additional data on a prod-

uct are generated, submitted and assessed. The applicant should notify the EMEA about his intention to request a conditional marketing authorisation as part of the "letter of intent" (see also section 3.1and 7.2 of NTA, Volume 2A, Chapter 4). (38)

Conditional marketing authorisations will be valid for 1 year on a renewable basis. Before expiry, the marketing authorisation holder shall apply for the renewal of the marketing authorisation.

Possible examples include products for life-threatening diseases, designated orphan medicinal products, and medicinal products for use in emergency situations. If an application for MA is submitted with an **incomplete dossier** for a MP meeting the conditions for a conditional authorisation, an obligation is imposed on the MAH to carry out further studies and to provide the results for an annual reassessment. Applications should contain, unless otherwise justified, quality and non-clinical data as for a normal authorisation.

The applicant will be required to finalise ongoing clinical trials or conduct new studies to verify a presumed "positive benefit-risk balance". Article 2 in the Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for MP falling in the scope of Regulation (EC) No 726/2004, providing the scope of the medicinal products which may benefit from a CMA:

- MP for human use as defined in Article 3 (1) and Art 3 (2) of Regulation (EC) No 726/2004 aimed at the treatment, prevention or medical diagnosis of **chronically or seriously debilitating diseases or life threatening diseases;**
- Medical products for human use designated **as orphan medicinal products;**
- MP for human use to be used **in emergency situations**, in response to public health threats duly recognised either by the World Health Organisation (WHO) or by the Community in the framework of Decision No 2119/98/EC of the European Parliament and of the Council Regulation of 24 September 1983. (66)

According to the Commission Regulation on the conditional marketing authorisation for MP falling in the scope of Regulation (EC) No 726/2004 a request for a Conditional Marketing Authorisation may be presented by the applicant at the time of the application referred to in Article 6 of Regulation (EC) 726/2004 accompanied by a detailed justification. The applicant may even make a request for CMA during the assessment procedure conducted by the CHMP of the Agency referred to in Article 7 (a) of Regulation (EC) 726/2004. (11)

It is noteworthy that also the CHMP may, during the assessment procedure of Article 7 of Regulation (EC) 726/2004, propose a CMA. This proposal has to be accompanied by detailed explanatory reasons and has to be communicated to the applicant.

The CMA can be applied for under the Accelerated Assessment procedure in accordance with Article 14(9) of Regulation (EC) 726/2004. Any request to, or proposal by, the CHMP for a CMA shall be made publicly available. The preconditions for the granting of a CMA include:

Committee finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. (65)

All specific obligations (SOs) according to Art. 7 of the Conditional Regulation and the period for their completion will be reviewed annually by the CHMP and shall be made publicly available. Once the missing data is provided, the CMA will become a "normal" marketing authorisation. (11)

Where a medicinal product has been granted a CMA in accordance with this Regulation, the information included in the summary of product characteristics and package leaflet shall contain a clear mention of that fact and the date on which the conditional authorisation is due for renewal.

Pursuant to Art 12 of the Conditional Regulation the guideline EMEA/CHMP/509951 covers the scientific application and the practical arrangements necessary to implement this Regulation. The timeline for a CHMP opinion is 90 days. (23, 66)

The periodic safety update reports provided for in Article 24(3) of Regulation (EC) No 726/2004 shall be submitted to the Agency and Member States immediately upon request or at least every six months following the granting or renewal of a CMA. Further information for the annual renewal is provided in the EMEA post-authorisation guidance. Authorisations issued under conditional authorisations are subject to SOs in respect of submitting further data, e.g. additional efficacy safety data. (67,68)

3.2.3. Assessment for authorisation under exceptional circumstances

Article 14(8) of Regulation (EC) 726/2004 permits authorisations to be issued in exceptional circumstances. This covers the situation where the **applicant is unable to provide the required data** due to the indication, which is rarely encountered. In such cases it will most probably not be possible to gen-

erate the full data and hence the authorisation will not be converted into a "normal" authorisation as is the case with conditional authorisations. The grounds for claiming exceptional circumstances are detailed in Directive 2001/83/EC, Art. 22, and must be based on one of the grounds of Directive 2003/63/EC, Part II. (11, 30), (see Figure 5).

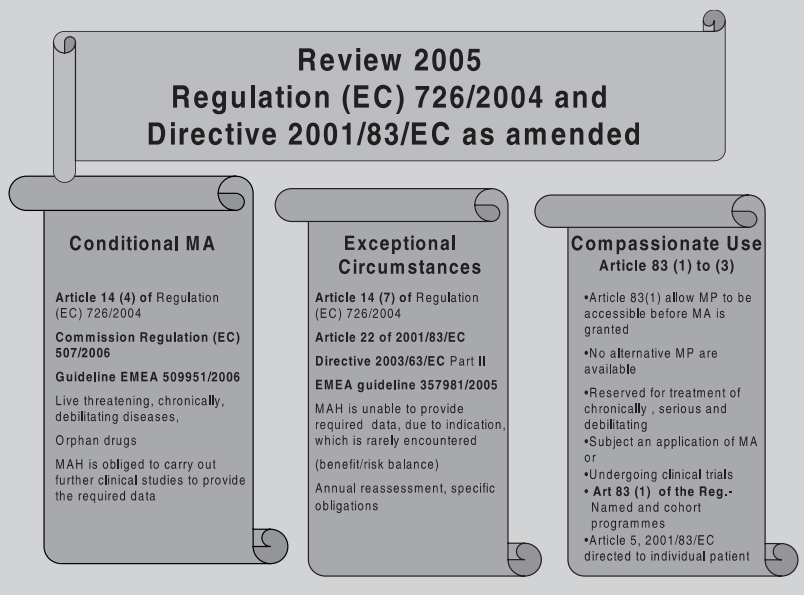

Figure 5. Temporary marketing authorisations of medicinal products

Conditions relating to the safety of the product, notification of adverse events, and the action to be taken are attached to the marketing authorisation. The continuation of the authorisation is linked to an annual assessment of these conditions. Authorisations issued under exceptional circumstances are subject to SOs in respect of submitting further data, e.g. additional efficacy safety data. The fulfilment of these SOs forms the basis of an annual reassessment. In addition, any authorisation may be subject to follow-up measures (FUMs) relating to post-approval commitments. A guideline on procedures for the granting of a marketing authorisation under exceptional circumstances (EMEA/357981/2005) pursuant to Article 14 (8) of Regulation (EC) 726/2004 was published by EMEA on 15 of December 2005. This type of authorisation is reviewed annually to reassess the risk/benefit balance and EMEA has developed a standard operating procedure for that assessment. (69)

3.3. Legal basis for EU decentralised marketing authorisation of MPs

For those medicinal products that are not eligible for the Centralised Procedure or where the applicant chooses not to follow that procedure, the system provides a **Mutual Recognition Procedure (MRP) since 1998 and a Decentralised Procedure (DP) since 30th of October 2005**.

Until 1995, the **National Procedure** was the only option to receive a marketing authorisation in the EU. Since 1995, a national procedure is no longer possible if an applicant intends to market a MP in more than one MS. Since then, a MRP has to be used by the applicant whenever an application for marketing authorisation for a medicinal product is to be extended to another or more Member States and the product does not fall under the mandatory scope of the CP. Today the national marketing authorisation procedure according to Article 17, Directive 2001/83/EC, should not take longer than 210 days and the duration of the rest of the authorisation procedures for MP was harmonised to that duration of time, excluding potential clock-stops to clarify issues and resolve deficiencies. Actually, the national procedure has been the basis for accumulating experience for the establishment of the other procedures.

With the Review 2005, the DP has been introduced as an additional procedure to the MRP. A marketing authorisation or the assessment report in one Member State (chosen as a Reference Member State - RMS) ought in principle to be recognised by the competent regulatory authorities of the other chosen Member States (Concerned Member States - CMSs), unless there are grounds for supposing that the authorisation of the medicinal product concerned may present a potential serious risk to public health. Both the MRP and the DP aim at facilitating the access to a single market by relying upon the principle of mutual recognition. Once the procedure for MRP or DP has been used, all **variations** to these medicinal products must use the procedure foreseen in the Variations Regulation 2003/1084. (13,41)

In addition, variations to “ex-concertation” medicinal products authorised by Member States following an opinion of the Committee for Human Medicinal Products (CHMP) given before 1st January 1995 are required to use the mutual recognition procedure. (69)

As a consequence of the review of the pharmaceutical legislation and in order to facilitate the access to medicines, MPs not authorised or with pending authorisation in a MS could be placed on the market for justified health reason if possessing authorisation in another MS. The review requests national legislative provision to be developed.

Co-ordination Group for Mutual Recognition and Decentralised Procedures - CMD (h). The Mutual Recognition Facilitation Group (MRFG) started its work in 1995 as an informal group. The aim of the MRFG was to

facilitate the work of the MRP and to support the CHMP at EMEA with best practice guides and procedures.

With the adoption of Directive 2004/27/EC, the Mutual Recognition Facilitation Group has gained an official status and has been renamed to coordination group. According to Article 27 of Directive 2001/83/EC the group consists of one representative per Member State. This new Co-ordination Group for Mutual Recognition and Decentralised Procedures - CMD (h) has been set up for "examination of any question relating to the medicinal products, involved in the MRP and DP. (Article 27 of Directive 2001/83/EC amending Directive 2004/27/EC to the Directive 2001/83/EC as amended) and to address procedural and scientific issues arising from the mutual recognition and decentralised procedures." (13,13,31)

The CMD (h) considers points of disagreement raised by a Member State in relation to the assessment report, summary of product characteristics, labelling and package leaflet of a medicinal product on the grounds of "potential serious risk to public health" within a MRP or DP. In the case of unsolved disagreement, the coordination group will refer the matter to the EMEA/CHMP for arbitration with a detailed reasoning for the disagreement.

The CMD (h) facilitates the establishment of dialogue between Member States through meetings and oral explanations and discusses any difficulties and problems in dialogue and seeks to overcome such difficulties between the RMS and CMSs involved.

According to the amending Directive the CMD (h) has to define a list of MPs for which a harmonised SmPC should be drawn up. This list takes into account proposals from Member States and the list shall be forwarded to the Commission once a year. The coordination group has a website "Heads of Medicines Agencies" (HMA) where recommendations, position papers, standard operating procedures (SOPs) and other documents are published. These documents are drafted and revised on a regular basis in order to improve and accelerate the market access of the medicines. (30)

3.3.1. Scope and exclusions of the decentralised system for authorisation of medicinal products

The scope of the MRP/DP covers all products which are not obligatorily subject to the CP as defined in Article 3 and in the Annex of Regulation (EC) 726/2004. Till May 2008, new chemical entities in the therapeutic indications for the treatment of autoimmune diseases, other immune dysfunctions, and viral diseases could be in the scope of the DP/MRP. After that date, the Commission has the right to extend the scope of the CP in any certain period of time, which will reflect the field of disease options of the MRP. (11,23,50)

According to Annex (4) of Regulation (EC) 726/2004, medicinal prod-

ucts with orphan designation fall under the mandatory scope of the CP and may not follow the DP/MRP after 20 of November 2005. Orphan medicinal products cannot be approved under the decentralised system because a significant therapeutic benefit will be provided (Article 3(3) and Annex (1) (4) of Council Regulation 726/2004). (See Table 4) (11,50)

A generic medicinal product of a reference medicinal product authorised by the Community may be authorised by the competent authority, which means that it will be a company's decision which way of MA will be chosen, DP or CP. Biosimilar products, however, fall under the mandatory scope of the CP due to the nature of their manufacturing process (Regulation (EC) 726/2004 and NTA-Volume 2a, Chapter 4). (11,38)

The MRP or DP may also be applicable to **extensions** of existing national marketing authorisations pursuant to Annex II of Regulation (EC) 1084/2003. However, before the applicant can use the MRP or DP, he has to ensure that the submitted dossiers are identical. This requires harmonisation of the already approved national SmPCs, package leaflet and labelling by using either national variations, an MRP, or a referral procedure under Article 30 of Directive 2001/83/EC. After a harmonised marketing authorisation in a MRP or DP has been granted, no further national extension will be possible. (31,41)

The MRP/DP is also required for **well-established use applications,** intended for authorisation in more than one Member State and for which the use of the centralised procedure is not mandatory.

Exclusions of medicinal product in the DCP and MRP:

- products falling under the compulsory scope of the centralised procedure pointed out in the Annex to Regulation (EC) 726/2004;
- homeopathic products pursuant to Articles 16(2) and 39 (2) of Directive 2001/83/EC;
- special, simplified registration of traditional herbal medicinal products which are **not** falling within the scope of Article 16d(1), cf. Article 16g(1) of Directive 2001/83/EC;
- products falling within the transitional arrangements for Cyprus, Lithuania, Malta, Poland and Slovenia upon their accession to the EU, based on Act of Accession, where the products are not authorised with the Directive 2001/83/EC (11,31,70).

3.3.2. The Mutual Recognition Procedure

The Mutual Recognition Procedure is based on a national marketing authorisation in one MS. The MAH/Applicant selects the MSs, Reference Member State (RMS) and Concerned Member State (CMS) where they intend to market the MP. The RMS plays an essential role in the MRP and acts as a scientific assessor of the documentation, as a regulatory advisor to the applicant,

and as moderator in the discussion between the applicant and the CMS. The RMS is the MS which has issued the marketing authorisation on which the MRP is based. An authorisation granted by the RMS in accordance with Article 28 of Directive 2001/83/EC should be recognised by the CMSs unless they identify a potential serious risk to public health. Within 90 days after receipt of a valid application, the RMS prepares a Draft Assessment Report (DAR) which shall be sent to the CMSs and to the MAH together with the approved summary of products characteristic (SmPC), labelling and package leaflet (PIL) (See Table 4). (See NtA, Volume 2A Chapter 2, February 2007). (47,71,72)

Emerging potential serious health issues should be communicated to the RMS as soon as possible and the CMSs should finalise their position ultimately by Day 50. The CMSs should clearly indicate whether comments should be regarded as a "point for consideration" or a "potential serious risk to public health". Both latter issues should be carefully screened within the national agencies and in case a CMS raises a "potential risk to public health" it shall give a detailed explanation of the reason for this position. All efforts should be exerted by the RMS in order to keep the dialog between the competent authorities and the applicant and to co-ordinate the communication and resolve any divergence. (72)

The duration of the MRP procedure is up to 420 days (National Procedure - 210 days, according to Article 17 (1) of Directive 2001/83/EC plus the time for the RMS Assessment Report - 90 days, plus 90 days for approval of the RMS-Assessment Report together with SmPC and PIL by the RMSs and the time for national implementation - 30 days), (see Figure 4, Table 4). (13, 31)

Commission Communication C28/2016 of 16 July 1998: Article 7a of Directive 65/65/EEC (now Article 18 of Directive 2001/83/EC), which became binding as of 1.1.1998, creates an obligation on MS to initiate a MRP independently of the course of action chosen by an applicant. From 1.1.1998 onwards, any application regarding a medicinal product already covered by an existing marketing authorisation in another Member State has to be submitted as a MRP. This procedure has to be considered as a "catch all" provision given to the Member States in order to secure an efficient implementation of Community law provisions dealing with the mutual recognition of national marketing authorisation. Differences between the SmPC already approved in one MS and the proposed SmPC, as part of the application under consideration in another EU country, do not automatically prevent the latter from triggering a MRP. If both products have the same qualitative and quantitative composition of the active substance and the same pharmaceutical form and these differences have no therapeutic implications they have to be considered as being the same and a MRP has to be followed.

The Commission position confirmed in March 1999 is that it is legally not acceptable for a concerned MS to recognise more than one MA granted by

the Reference MS. Recommendations on multiple applications (for the purpose of co-marketing) were set up for better covering the market with certain MPs. For practical purposes, a duplicate application is defined by reference to the first application or MA (same legal basis, same dossier, same or different MAH, but different trade name). (73, 31)

3.3.3. The Decentralised Procedure

A new procedure, **the Decentralised Procedure (DP),** is applied to medicinal products that have not been previously authorised in the EU since 30th October 2005. The DP has been created in addition to the MRP and can be applied to MP not falling under the mandatory scope of the CP, i.e. like the MP under MRP. The DP, pursuant to Directive 2004/27/EC and Directive 2001/83/EC, as amended, is used to obtain a marketing authorisation in more than one MS when the MP has not yet received a marketing authorisation in the EU. Under the DP, the applicant submits identical dossiers to all relevant Member States. The applicant in accordance with Article 28 of Directive 2001/83/EC normally initiates the procedure. Once the DP is triggered by the applicant, the DP timelines have to be followed. All details for the DP are comprehensively presented in NtA, Volume 2a, Chapter 2. (31,47)

The DP (NtA, Volume 2a, Chapter 1, issue 4) is divided into four steps: Pre-procedural step with the Validation phase, Assessment step I and Assessment step II including discussion at the CMD (h), if needed, and a final national phase. According to the standard operating procedure (SOP) of **DP the Assessment step I** corresponds to the 120-day period for preparing the Draft Assessment Report (DAR) and draft SmPC, draft PIL, and draft labelling. The RMS forwards the Preliminary Assessment Report (PrAR) with the comments on SmPC, PIL, and on the dossier to the CMS and the applicant within 70 days after the start of the procedure. (74) (Table 4)

By day 100, CMSs should communicate their comments to the RMS and the applicant and if any issues for “potential serious risk to public health” are identified, they should first be carefully screened within the national agencies. If a CMS raises a “potential serious risk to public health”, it shall give a detailed explanation. If consensus is reached that the product is approvable and the comments can be easily solved, the RMS forwards these comments to the applicant at day 105. At this point in time, the RMS stops the clock and restarts the clock on day 106 after receipt of the response. The period of time assigned to the clock-stop period will be determined in agreement with the applicant depending on the complexity of the questions raised but will not exceed a recommended period of 3 months unless duly justified. (NtA, Volume 2a, Chapter 2, issue 4.3.2) At day 120, the RMS may close the procedure if consensus is reached, which continues at national level. (75)

During the Assessment step II from day 120 till day 210 according to Article 28 (4) of Directive 2001/83/EC, as amended, each CMS will recognise the marketing authorisation and the summary of product characteristics, package leaflet, and labelling granted by a MS within a 90-day period. This period includes discussion at the CMD (h), if needed. The RMS also uses the meeting of the CMD (h) as an opportunity to discuss major issues that have arisen during the procedure and seeks assistance in solving the issues. The CMSs have 90 days to recognise the decision of the RMS or the application will continue into an arbitration procedure (the total time of a DP procedure is herewith 240 days compared to the 420 days for MRP), When disagreement between the RMS and CMSs arise, the procedure is forwarded to the CMD(h) If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly.

If the Member States fail to reach an agreement within the 60-day period, the EMEA shall be immediately informed, with a view to the application of the procedure under Articles 32, 33 and 34 of Directive 2001/83/EC. A detailed statement is provided to EMEA with the matters on which the Member States have been unable to reach agreement and the reasons for their disagreement. A copy shall be forwarded to the applicant. The procedure described in Chapter 3 of the Notice to Applicants should be followed using the appropriate form to notify the EMEA. (38,75)

3.3.4. National Step of the decentralised system of marketing authorisation

Both procedures, MRP and DP, are presented in NtA, Volume 2a, Chapter 2. Some specific guidance is presented in the CMD (h) “Best Practice Guide for the Referent Member State in MRP and DP Procedure” on the HMA/CMD website. This guide presents the procedure for operating MRP and DP in all phases of the marketing authorisation process and is intended to improve the processes in order to accelerate market access. In both procedures, the NCAs shall adopt a national decisions 30 days after the RMS closes the procedure. However, this is only possible if the applicant submits high quality national translations of the SmPC, PIL and labelling not later than 5 days after the procedure is closed. The product information should be a faithful and understandable translation of the final harmonised position. The ‘blue box’ concept for necessary adequate national information on the label and package leaflet is permissible and should be taken into account when finalising national translations. (71,75)

Table4. Comparison between MRP acc. Directive 2001/83/EC and MRP/DP acc. Directive 2004/27/EC and Directive 2001/83/EC as amended

Issue	Mutual Recognition Procedure (MRP) pursuant to 2001/83/EC	Mutual Recognition Procedure (MRP) Decentralised Procedure (DP) 2004/27/EC and 2001/83/EC as amended	Comments and conclusions on the changes - DP/MRP- 2004/ 27/EC
National assessment process	**National marketing authorisation is needed for MRP (210 days)**	**MRP - National MA is needed for MRP DP - National MA not needed for DP**	For the DP no requirements for national approval are needed
Scope of the Procedure MRP or DP	**MP under MRP** (MP essentially similar to RP under MRP) - new substance, except in Annex Part A, Reg. 2309/93 except - MP of Annex Part B Reg. (EEC) 2309/93, Orphan MP	**MP allowed under DP/MRP** - generic homeopathic - herbal MP - immunological MP - blood medicinal products - till May 2008 autoimmune diseases, immune dysfunction, viral diseases possible	With the Review 2005, the scope of the MRP and DP shall be within NtA 2a, Chapter 2 In consequence, the scope of the MRP/DP has been narrowed. (med. Product from Annex 1 of Reg. 2004/726 are excluded), orphans already authorised,
Submission of the Application of MP	To the RMS, where National authorisation is issued and to choose CMS's	-For MRP: to RMS where national authorisation is issued and to chosen CMS's -For DP: to the RMS and CMS's	Different trade Names allowed in MRP and in DP
Type of applications to be submitted	**Stand-alone application** Bibliographic applications Mixed application **Abridged application** Inform consent application **Essentially similar to RP under CP/MRP**	**Stand - alone application** Bibliographic application Mixed application **Abridged application** Inform consent application **Generic application to RP under CP or CP/MRP**	- Serious positive approach for generic application, when RMP is not available in MS where the product is applied for - application two years before data exclusivity expiration
Fee	Fee payment to the RMS + to each CMS's	Fee payment to the RMS + to each CMS's	No change in the legal issue
Number of Dossiers	To RMS and to CMSs according NtA 2A, Chapter 7	To RMS and to CMSs according NtA 2A, Chapter 7	No change in the legal issue
National Ass. process	**MRP-National MA shall be finished before start of the procedure**	**MRP- National Procedure should be finished before start DP - No national procedure is needed before start the procedure**	National Procedure is not needed before starting DP
RMS sends an Assessment Report, SmPC, PIL to CMSs	**MRP- within +90 days Art. 28**	**MRP- within +90 days DP - RMS within 120 days Art. 28 (3)**	Harmonisation process of SmPC, PIL parallel with the Assessment Report
Total duration of the procedure	**MRP- National auth. (210days) RMS - AR (90days) + CMSs AR (90 days) + National phase 30 days = 420 days**	**MRP - National auth. (210days) + RMS - AR (90days) + CMSs - AR (90 days) National phase 30 days =420 d DP 120 days AR + 90 days CMS AR + 30 days National phase =240 days**	MRP - 420 days DP - 240 day DP - 180 days shorter than the MRP

3.3.5 Comparison of the MRP and DP

Table 4 provides a comparison of the MRP and DP. The advantage of the DP clearly is the shorter period of time for the DP 240 days compared to 420 days for the MRP. However, basically the scope of both decentralised ways of authorisation and the type of application is the same. The advantage of the DP is that no national marketing authorisation is needed as a first step as for the MRP. It is thus possible for all MS involved in the procedure to clarify outstanding issues and divergent positions before the first marketing authorisation has been granted. This early involvement of CMSs in the assessment process may help to avoid arbitration procedures. On the other hand, once a national marketing authorisation has been granted, no DP is possible, the MRP becomes mandatory. Another positive reason for both procedures MRP/DP following the review in comparison to the MRP before the end of 2005 is the fact that the harmonisation period of SmPC and PIL is now done during the assessment period. In the national phase only linguistic changes are possible, which shall not influence the content of the SmPC and PIL accepted in the harmonisation period.

The fees for each MRP and DP procedure depend on the MS involved, some MSs have different fees for the MRP and DP. The fees range significantly between MSs and the wording of the MRP/DP procedure is very broad from MS to MS. However, this is subject to MS decision. In most cases, the fees for a CP may be more attractive for a product to be marketed in the entire Community compared to the use of MRP or DP.

By elaborating and publishing procedures and requirements for both MRP and DP, the CMD(h) has significantly contributed to facilitating the understanding of the intention of the respective Directives and Regulations as regards these two licensing procedures.

3.4. Community Referrals

If the CMSs do not recognise the decision of the RMS, the application will continue into an arbitration procedure according to Directive 2001/83/EC as amended. These are the commonly called Community “referrals”, which have been developed since the MRP and the CP have been introduced. At the end of the procedure, in case of a positive outcome, the CMSs will have to issue national marketing authorisations. Other Member States not directly concerned at the time of the decision are also bound as soon as they receive a MA application for the same product. (19)

Pursuant to the amended Directive 2004/27/EC many new steps have been introduced for improving and shortening these procedures. (13)

3.4.1. Type of arbitration

An important purpose of the EU legislation relating to the MA for the MP is the harmonising of decisions by the different MSs. For this reason, Directive 2004/83/EC provides different types of arbitration procedures. In the various arbitration procedures, CHMP should provide an opinion to the EU Commission, which takes a binding decision for the MSs (see Table 5).

In accordance with Article 29 of Directive 2001/83/EC as amended, where one or more MS cannot recognise an authorisation already granted in a MRP or a final assessment and product information prepared in a Decentralised Procedure due to a "potential serious risk to public health", the points of disagreement shall be referred to the CMD (h). The consideration of issues by the CMD(h) was introduced in 2005 with the main idea to prevent the CHMP arbitration process. Prior to that time, issues raised in referrals often remained unresolved because the applicant could withdraw the application in the dissenting concerned Member State, thus preventing an arbitration and thus allowing the same issue to cause problems repeatedly. (76)

Where the Member States concerned by the procedure fail to reach an agreement within the CMD (h), the matter is referred to the CHMP for application of the procedure laid down in Articles 32 to 34 of Directive 2001/83/EC. This referral is automatic in the sense that once a Member State has raised a concern on the grounds of potential "serious risk to public health" within the meaning of Article 29(1), withdrawal of the marketing authorisation application in that Member State does not prevent the concern from being analysed within the CMD(h) and, in absence of an agreement therein, referral to CHMP. The expression "potential serious risk to public health" is defined in a guideline which was issued by the Commission in 2006. (72)

The harmonisation of the initial authorisations is maintained through the MRP/DP with respect to post-authorisation regulatory activities e.g., variations, renewals.

The arbitration procedure according to Article 30 is based on several applications, which are submitted as per Articles 8, 10, and 11 of Directive 2001/83/EC as amended. National authorisations in more than one Member State were possible until 1st of January 1998, which often resulted in divergent decisions. Article 30 is used to initiate the prospective harmonisation of SmPC of the selected medicinal products. The different national procedures of the reference product may impede the MA of the generic products, whereby differences will make the process rather long and complicated. A Working Party had facilitated the above process and determined the criteria for these medicinal products. Historically, the former Working Group (MRFG) established in 2001 provided information on the aims and timelines for prospective SmPC harmonisation and the first referrals concerning harmonisation were initiated in

November 2002. The remaining types of referrals **according to Articles 31, 35-36** are presented in Table 5. (31)

3.4.2. Duration of the Community arbitration process

Referring to the changes in Article 27 of Directive 2004/27/EC, if a MS does not agree to recognise the authorisation of the reference product on the grounds of serious potential "risk to public health" the matter will initially be reviewed by the CMD (h). If issues cannot be resolved within 60 days by the CMD (h), the matter will be referred for arbitration to the CHMP. The process is initiated by the Committee issuing an opinion within 60 days. This period has been shortened compared to the previous pharmaceutical legislation of 2001 where this period was 90 days. Those Member States that are prepared to approve the MP under consideration can already issue an authorisation without waiting for the outcome of the arbitration procedure. The CMD(h) established overview of the timetable of the procedures for MRP/DP and standards according to the amended Directive 2001/83/EC.

Compared to the previous arbitration process, according to Articles 32, 33, and 34 of Directive 2001/83/EC, the CHMP process without such a CMD (h) consensus step was 180 days plus additional 30 days for national implementation. Now, pursuant to Directive 2004/27/EC, the Committee opinion step and the steps for the Commission decision are shortened by 68 days: Articles 32, 33, and 34 of Directive 2004/27/EC compared to the previous referral process. The arbitration process and the timelines defined in the new legislation of Directive 2004/27/EC compared to the arbitration process according to Directive 2001/83/EC are presented in Table 6.

Many new aspects in Directive 2004/27/EC provide advantages in terms of shortening the period of arbitration and resulting in accelerating the authorisation of the medicinal products. When consensus is reached in the CMD (h) within 60 days, the procedure will be followed by a national authorisation process, which should not be longer than 30 days. In this case the duration of such DP ((with CMD (h) consensus)) becomes 240+60 (300) days and the duration of the MRP ((with CMD (h) consensus)) is 420 +60 (480) days.

Such arbitration period for the MP will be 90 days (Directive 2004/27/EC) compared to the referral with Commission decision where 172 + 30 days (National step) after the MRP/DP period (390/210 days, without National Phase) have to be counted.

The arbitration procedure in the previous legislation, according to Directive 2001/83/EC, was 180 days + 30 days National Phase and today such process even with the CMD (h) step takes 6 days (5%) less. The comparison of both referral procedures as applicable in 2001 (Directive 2001/83/EC) and 2005 (Directive 2004/27/EC) is presented in Table 5. The current procedure for the

Commission step is with 68 days (38%) shorter than the previous one due to Directive 2001/83/EC. (13,31)

3.4.3. Transparency of the Community referral

According to Article 21 (3) and (4) of Directive 2001/83/EC, as amended, the competent authorities shall make publicly available a Public Assessment Report (PAR) of marketing authorisations issued via the MRP or DP. The competent authorities shall draw up an Assessment Report and comment on the file as regards the results of the pharmaceutical and preclinical tests and the clinical trials of the MP concerned and it shall update whenever new information becomes available which is of importance for the evaluation of the quality, safety, and efficacy of the MP. The competent authorities and the Agency shall make publicly accessible without delay the Assessment Report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. Together with the Assessment report, the Commission established a List of referral for human medicines, which is publicly available on the EMEA and Commission website. (31,77)

Table 5. Arbitration procedures in Directive 2001/83/EC compared to the arbitration procedures in Directive 2004/27/EC

Referral Categories	Directive 2001/83/EC	Directive 2004/27/EC and 2001/83/EC as amended
(Article 29) **Referrals in the decentralised system of MA** **(Related to risk to public health)**	Divergent decisions for the assessment report, SmPC, PIL or its suspension or revocation (Art. 8, 10 (1) (a) (i), (ii),(iii), 11) **MS, Commission, Applicant/ MAH may refer to CHMP,** (Art. 32, 33 and 34) Art 1 (28) risk related to efficacy, quality, safety	Divergent decisions for the Assessment Report, SmPC, PIL or its suspension, or revocation, (Art. 8, 10, 10a, 10b 10c and 11) **MS, Commission, Applicant/ MAH** may refer to CHMP, (Art. 32, 33 and 34) Art 1 (28) more specified; positive effect to risk-benefit balance and EMEA guidelines
(Article 30) **Divergent decision referral** (prospective harmonisation of SmPC)	Divergent decisions for the assessment report, SmPC, PIL or its suspension or revocation, Art. 8, 10 (1) 11 **MS, Commission, MAH** may refer to CHMP, (Art. 32 – 34) **MRP Working Party –** timelines for prospective SmPC harmonisation	Divergent decision, suspension, revocation of MA on MP (Art. 8, 10, 10a, 10b 10c and 11) **MS, Commission, Applicant, MAH** may refer to the CHMP, (Art. 32-34) **Coordination Group CMD(h)** for harmonisation purpose MSs shall forward to the CMD a list of MP
(Article 31) **Community Interest Referrals**	MS, Commission, applicant, or MAH may start referral for pharmacovigilance purposes: - Before decision is reached for MA	MS, Commission, Applicant, or MAH referral pharmacovigilance purposes - Before decision is reached for MA **-therapeutic class could be involved** **- certain specific part of the MA to the CHMP (Art. 32, 33 and 34)**
(Article 35-37) **Follow up referrals - Arbitration where harmonisation has already been achieved by Community procedure**	MS or MAH may start referral for: „ex-concertation" MP, MP which have to follow the MRP Variation of MP after MRP	MS or MAH may start referral: „ex-concentration" MP, which therefore have to follow the MRP Variation of MP after MRP

Table 6. Arbitration procedures in Directive 2001/83/EC Compared to arbitration procedures in Directive 2001/27/EC

Step of the Referral Procedure	**Directive 2001/83/EC (before 30th Oct 2005) MRP, CP**	**Directive 2001/27/EC (after 30th of Oct. 2005 .) MRP/DP, CP**
1.Structure at the EMEA involved in the referral process	MRP Working Party (MRFG) provided information on the aims and timelines for prospective SmPC	Agreement in the Co-ordination Group In 60 days agreement between the CMD (h) member (Art 29. 3) CMs adopt decision (30 days national MA)
2. If CMS does not accept the Ass. Report - start of Arbitration procedure	Start of the procedure **directly via the agency though CHMP**	(CMD 60 days) in case of disagreement arbitration procedure via the Agency (CHMP) Those CMSs who agree with decision may authorise the product ahead of arbitration.
3. CHMP Opinion (Art. 32)	1. CHMP opinion within Ass. Report, SmPC, PIL within 90 days **- authorisation in 30 days** 2. **Negative CHMP opinion -** within 15 days **appeal, in 60 days** the ground of the appeal. **Within + 60 (120) days CHMP final opinion**	1. **Reasoned CHMP opinion**, Ass. Report, SmPC, PIL within 60 days **(30 days shorter)** 2. **Negative CHMP opinion -** within 15 days **appeal, in 60 days** the ground of the appeal. **Within + 60 (120) days CHMP final opinion and procedure like in 1.**
4.EMEA Referral opinion, **Ass. Report, SmPC, PIL** send to the Commission	In **+ 30** days Shall be provided (altogether 120 days)	In **+ 15 days(15 days shorter)** Shall be provided (altogether 75 days) **(altogether 45 days shorter)**
5. Written observation of the MSs to the Commission Draft Decision	In **30 days** Shall be provided (altogether 150 days)	In **+ 22 days (8 shorter)** Shall be provided (altogether 97 days **(altogether 53 days shorter)**
6. Final Commission Decision	In **30 days (Art. 34)** Shall be provided (altogether 180 days) If MS raises important new questions of a scientific or technical nature, the matter referred back to the Agency and the procedure is repeated as per 32 (4). Decision based on 34 (2) 121 (2), Art 5 of 1999/468/EC. By Negative CHMP opinion or MSs, company could appeal	**In +15 days** (Art 34)**(15 days shorter**) Shall be provided (altogether 112 days) **(altogether 68 (38%) days shorter)** If MS raises important new questions of a scientific or technical nature, the matter is referred back to the Agency: Art.32 (4). Decision based on 34 (2) 121 (2), Art. 5 of 1999/468/EC. By Negative CHMP opinion or MSs, company could appeal

3.5. Legal basis of Simplified Registration Procedures

The legal basis for the Simplified Registration Procedures for homeopathic and herbal medicinal products (traditional-use registration) is presented in Articles 14, 15, and 16a of Directive 2004/24/EC, respectively. A Simplified Registration Procedure for homeopathic medicinal products has been introduced since 2001, according to Directive 2001/83/EC. In the amended Directive 2004/24/EC to the Community Code specific provisions applicable to traditional herbal medicinal products were established, which allow a Simplified Registration Procedure for them based on specific criteria. In Figure 6, the criteria of the Simplified Registration Procedure (SRP) for the both classes of MPs are presented. (19,20)

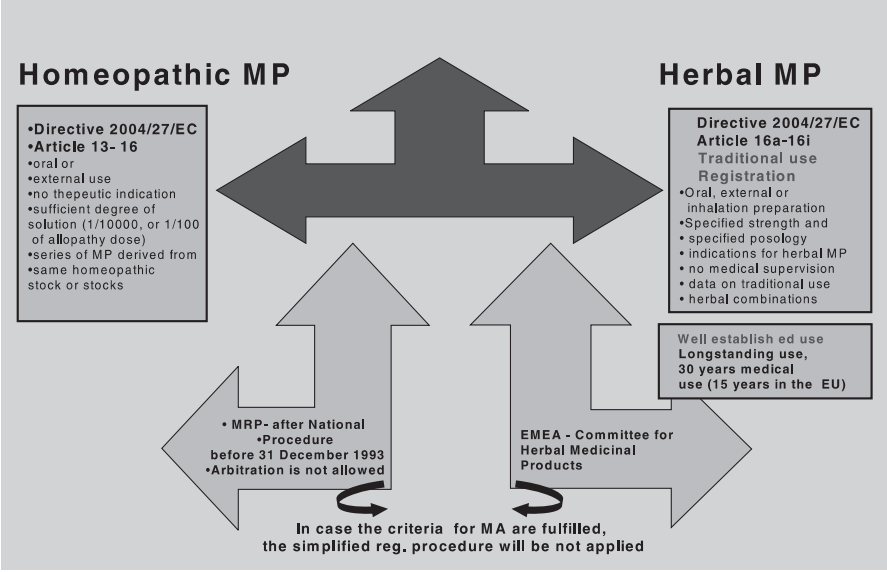

Figure 6. Criteria for the EU- Simplified Registration Procedures (SRP) for homeopathic and herbal medicinal products (Directive 2004/24/EC)

3.5.1. Simplified Registration Procedures for homeopathic medicinal products

Until the introduction of Directive 92/73/EEC relating to homeopathic medicinal products, the European legislation did not require marketing authorisation for these products. The different marketing authorisation procedures were on a country level and till 1992 there were no such EU requirements. The provisions for homeopathic MPs in Directive 92/73/EEC were incorporated in Directive 2001/83/EC and later in 2004/24/EC. (19,20,78)

For the first time, a definition for homeopathic medicinal product has been provided in Directive 92/73/EEC. A homeopathic medicinal product is defined as "any medicinal product prepared from substances called homeopathic stocks in accordance with a homeopathic manufacturing procedure, described by the European Pharmacopoeia, or in the absence thereof, by the pharmacopoeias currently used officially in the Member State". According to the same directive, MS had to ensure that homeopathic medicinal products manufactured and placed on the market within the Community were administered orally or externally and no specific indication appeared on the labelling, the PIL had to be labelled with the specific information presented in Article 7. (78)

The reason for these requirements was that the normal licensing procedures were not suitable for homeopathic medicinal products as the action of homeopathic medicinal products is not based on the pharmacological action of the substances but rather on specific homeopathic principles and "normal" clinical trials are not compatible with the principle of homeopathic medicine. Till end 2005, homeopathic medicinal products were authorised on a purely national basis according to the EU legislation. Since 2001, according to Article 14 (1), Directive 2001/83/EC, a Simplified Registration Procedure (SRP) for homeopathic medicinal products has been applicable. The requirements described in the Community Code for this procedure are based on the assumption of the guaranteed safety of the products in accordance with their dilution (not more than 1/10,000 of the mother dilution or more than 1/100 of the mother tincture) and the absence of a defined medical indication.

The requirements of the registration procedure differ in many ways from the "normal" MA procedure. There are two ways for reaching the market in the EU:

1. Through a Simplified Registration Procedure pursuant to Directive 2004/27/EC;
2. Through a marketing authorisation procedure where the requirements are applied to allopathic medicinal products, with applied clinical data.

The Simplified Registration Procedure, of Article 14, will go through the Mutual Recognition Procedure, Article 28 and Article 29 (1) to (3). However, the arbitration procedure of Article 29 (4) to (6) of the same Directive will not be applicable according to the Review 2005. For other homeopathics with indication for self-treatment a proof of efficacy should be assumed or proved and Articles 10, 10a, 10b, 10c of the same Directive should be applied. The requirements for the SmPC for these medicinal products are the same as for the other MPs. (13,31)

3.5.2. Simplified Registration Procedures for traditional herbal medicinal products

In 1992, the CPMP published a List of Herbal Drugs with serious risks. The List was prepared and adopted by the CPMP and it was published by the European Commission in October 1992. The document (EMEA/HMPC/246736/2005) was considered by the previous Herbal Medicinal Products Working Party between 1997 and 2004 and a strategy for updating the document had been prepared. The CPMP considered that this list was a useful source of information on plants with intrinsic safety risks and therefore it had decided to be published. (79)

Member States had adopted divergent national requirements for herbal medicinal products (HMP), which were presented in a report prepared by AESGP for the Commission in 1999, showing different experience in the different MSs. This report also served as an attempt for comparison of the legal requirements for herbal medicinal products in the EU Member States. In almost all MS, the HMP were considered as medicinal products and they were in principle subject to the general regulations for medicines as laid down in the various national medicines laws. The conclusion of this report stated that two categories existed in many MSs; however there were major discrepancies between the MSs in the classification of the individual herbal drug preparations and products into one of these categories and in their requirements for obtaining a marketing authorisation. (80)

Therefore, the cumulated experience in the field of herbal medicinal products, the amended Directive 2004/24/EC and the Directive 2001/83/EC, as amended, has come into effect. Article 1 (30) provides for the first time a definition of HMP in order to harmonise this issue within the EU countries "Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations". (31)

Directive 2004/24/EC had to be implemented by Member States by 30 October 2005. Herbal medicinal products (HMP) for which sufficient evidence is available to support the quality, safety, and efficacy of the product must apply for a full marketing authorisation. This can be done on the basis of published literature if sufficient to support the "well-established use". The legislation also contains a provision of a bibliographic application under Article 10 (1) (a)(ii) of Directive 2001/83/EC. (19,20)

According to Article 16a and 16c of Directive 2001/83/EC as amended there is also a special Simplified Procedure for traditionally used herbal medicinal products, which allows the registration of herbal medicinal products without requiring particulars and documents on the tests and trials on safety and effi-

cacy and there is a sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the Community. (31)

3.5.3. Committee on Herbal Medicinal Products (HMPC)

Directive 2004/24/EC, Article 16h, established a Committee on Herbal Medicinal Products (HMPC), which took over the tasks of the CHMP with respect to herbal medicinal products and started its work on 23 September 2004. (20)

Formerly, the CHMP was aided in its work on herbal medicinal products by its Herbal Medicinal Products Working Party (HMPWP), initially established as an ad hoc Working Group on Herbal Medicinal Products. The main task of the ad hoc Working Group in 1997/1998 was the protection of public health by preparing guidance intended for successful mutual recognition of marketing authorisation in the field of herbal medicinal products and restricting the arbitration to a minimum (EMEA/HMPWP/25/99). Further to the report on the activities in 1997/1998 of the ad hoc Working Group on Herbal Medicinal Products, the Management Board endorsed the present mandate for the group to become a Working Party of the EMEA in 1999. The Working Group was established on the request of the European Parliament and the European Commission and later became a Working Party. (81,82)

One of the tasks of HMPC is the preparation and the publication of Community herbal monographs in accordance with a standard procedure for traditional herbal medicinal products and a procedure for herbal products with well-established medicinal use. They will be based on a standard template detailing information such as name, constituents, clinical particulars and pharmacological properties. Whenever such monographs have been adopted they must be used as the basis for registration assessment. Furthermore, when new monographs are adopted, the registration holder will be required to amend the registration dossier to comply with the new monograph. Where no such monographs have been established, other appropriate monographs, publications or data may be referred to. (83)

The Herbal Committee, established pursuant to 2004/24/EC, has the discretion, in individual cases, to draw up an opinion on the adequacy of the evidence and of the longstanding use of the product or of the corresponding product, less than 15 years usage of HMP in the EU, when justified. The HMPC is responsible for the various tasks concerning the simplified registration and authorisation provided in Directive 2004/27/EC and in Regulation (EC) No 726/2004, including involvement in referral procedure concerning such products. (11,20)

3.5.4. Legal Basis for marketing authorisation of herbal medicinal products

Herbal medicinal products may be licensed when there is sufficient evidence relating to the quality, safety and efficacy of the product to support a full application for a marketing authorisation. This will normally apply when there is sufficient published literature to support the "well-established use" provision as a bibliographic application under Article 10 (1) (a)(ii) of Directive 2001/83/EC and in the updated version of 2004 of Article 10 a. (19, 31). This is usually done as a bibliographic application under the same article. With regard to efficacy data for a bibliographic application a points–to-consider document provides a classification system linking the extent of data required to the nature of the indication, (EMEA/HMPWG/32/99). A further guideline provides information with regard to combination products (EMEA/HMPC/166326/2005). (84,85)

For many herbal medicinal products sufficient published data is not available to support a bibliographic application. For such products there will be no requirement to provide information relating to efficacy (Article 16c of Directive 2004/24/EC). Instead, the efficacy will be supported by evidence of long term use supported by evidence relating to safety and quality. (20)

3.5.5. Traditional-use registrations

Traditional-use registrations according to Article **16a** of Directive 2004/24/EC will be restricted to herbal medicines that are intended for use without the intervention of a medical practitioner. Registrations will also be restricted to herbal medicines that are taken orally or are for external use or inhalation. Registration of traditional herbal medicinal products combined with vitamins or minerals may be possible where there is evidence of safety and where the action of the nutrient is ancillary to that of the herbal active ingredients. The applicant will be required to provide evidences relating to traditional use, quality, and safety in accordance with the requirements detailed in Articles 16b and 16c of the same Directive. The provisions will in effect derogate from the standard efficacy requirements as justified by the product's safety profile and a traditional use. Bibliographic or expert evidence will be required.

This must relate to the product concerned or "a corresponding product" to support the traditional use period (Article 16 c (2) of Directive 2004/27/EC). A Member State will be able to request the Committee to provide an opinion on the adequacy of this evidence. A corresponding (or comparable) product must have the same active ingredients; the same or similar intended purpose; the same or similar route of administration; equivalent strength and posology. The number or quantity of ingredients may be reduced during the qualifying period of traditional use. A bibliographic review of safety data together with an expert report will be required and when being requested by a competent authority, data

necessary for accessing the safety of the product will have to be provided. An important point, in relation to safety, is that the product must be suitable for use without medical supervision. (13)

The format for an application for a marketing authorisation must be based on the Common Technical Document. For a bibliographic application, the requirements as pointed out in the NtA: Modules 1, 2, and 3 should be fulfilled, Commission Directive 2003/63/EC. The results of non-clinical tests and clinical trials (Modules 4 and 5) may be replaced by references to published scientific literature. Guidance for non-clinical and clinical data is available on the application of non-clinical tests to herbal medicinal products with long-term marketing experience. (20, 28)

The scope of the new provisions and criteria for traditional use registration of Article 16a (1) details the criteria which herbal medicinal products will have to meet in order to be eligible for the simplified procedure: (20)

- HMP must have indications exclusively appropriate to traditional herbal medicinal products and be intended for use without a prescription;
- HMP must be exclusively for administration in accordance with a specified strength and posology;
- HMP must be for oral, external, or inhalation use; a period of thirty years traditional use must have elapsed including at least 15 years within the Community.

The data on the traditional use of the HMP must be sufficient; in particular, the product must be proven not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the product must be plausible based on long-standing use and experience.

3.5.6. Facilitating Mutual Recognition Procedures for herbal medicines

For some herbal products “core-data” (previously called core-SmPCs) are available. The basis for these are the monographs produced by the World Health Organisation (WHO) and ESCOP (European Scientific Cooperative on Phytotherapy). A concept paper has been issued which explains the approach taken in drafting core-data based on the level of scientific evidence. As explained in the SOP, these core-data documents are intended to facilitate Mutual Recognition procedures for herbal medicines (EMEA/HMPWP/41/01). In the future, consideration should be given to any relevant Community herbal monographs. The European Pharmacopoeia provides many monographs relative to herbal products and it is also possible to obtain certification of the European Directorate for the Quality of Medicines & Healthcare (EDQM). (86,87)

The Mutual Recognition Procedure will apply for products for which reference to a Community monograph or to the List of herbal substances are applicable. For products where this is not the case, each Member State shall be required to take “due account of registrations granted by another Member State” (Article 16d). Each Member State shall make a decision on a valid application ((Article 16g linking to Article 17(1)). Requirements relating to post-marketing regulatory activities such as variations (e.g. to keep the quality section up-to-date), renewals and pharmacovigilance will apply in the same way as for non-herbal medicinal products ((Article 16g (1) Directive 204/27/EC)). Derogation is given for traditional herbal medicinal products, which were already on the market on the 30-Apr-2004 (date of entry into force of Directive 2004/24/EC); for these products Member States must apply the provisions of the Directive by 30 April 2011. (20)

4. Discussion on challenges in the Review 2005 for accelerated access of medicinal products

The revised Regulation (EEC) 2309/93, which became Regulation (EC) 726/2004 and both amending Directives 2004/27/EC and 2004/24/EC to the Community Code 2001/83/EC have significant impact on the European Medicines Agency, on the EU regulatory authorities and on the industry as well. In general, the rationale underlying both Centralised and Decentralised Procedures provides a strong foundation for future progress to a harmonised and efficient regulatory environment**.** There is a strong desire of both applicants for marketing authorisations and the competent regulatory authorities to maintain the parallel systems because of their different attributes. (16,17)

All changes introduced by the Review 2005 were introduced after many remarks of the Commission Report in 2001 based on many discussions and various consultations with the interested parties. Nevertheless, both innovative and generic industries were in general highly complimentary about the expertise and efficiency of RMS in the period 1998-2004. One of the aspects that came in for most criticism in the Commission for the CP report was the time required for the Commission's decision-making process. It was noted that the time required for the entire authorisation procedure amounted to a quarter or even a third of the total time required for the entire authorisation procedure. On the other hand, the operation of the Mutual Recognition Procedure has undergone substantial improvement since 1998. However, several aspects were targeted for criticism although the system has in general terms produced tangible results. The main problem which has been criticised is that Member States re-evaluate dossiers and – despite the procedure's name – the other marketing authorisations were actually not "recognised". When the national authorisation granted by the RMS was not accepted via "mutual recognition" by a CMS, which should lead to Community arbitration, firms often withdrew the request for authorisation in that CMS, effectively ending any chance of a Community-wide resolution or dispute. Another serious weak point was that once objections relative to potential serious risk public health have been raised, it often proved to be quite difficult to reach an agreement between the dissenting Member States. So far it was stressed out that the evaluation carried out in the MRP can be less robust than that occurring through the centralised system and problems have also been reported with respect to the length of the arbitration procedures according to Directive 2001/83/EC. However, there was no real perception that

either the centralised or decentralised system has failed to provide a high degree of safety for patients in relation to the MP on the EU market. (17,88)

Both the Centralised and Decentralised Procedures were perceived to have contributed in a qualitative and quantitative sense to the creation of a harmonised Community market for medicinal products reaching the patients as soon as possible. Both systems demonstrate the willingness of regulatory authorities to operate within the decentralised procedure according to the centralised principles. Examples for this statement are the transparency and the SmPC and PIL harmonisation process within the new MRP/DP and arbitration procedures.

The overall status of applications till the end of 2006 has shown a total of 4062 MR procedures and arbitrations on 28 new drug applications and 23 variations. Out of the 10 MRP procedures referred to CMD (h) in 2006, only 2 were forwarded to CHMP for arbitration. Also, all new applications approved under the Centralised Procedure granted by the European Commission are a total of 318 MAs out of 502 submitted applications, in the period from 1995 till January 2006. During the same period of time, 100 withdrawals prior to opinion were made and in 8 cases the Commission decided not to allow these medicinal products to be placed on the EU market in spite of a positive CHMP opinion. (22,88)

The statistical evaluation demonstrates that ten times more applications have been filed in the MRP than in the Centralised Procedure although the period of time evaluated is ten years for MRP and 12 years for CP, respectively. However, expanding the scope of the Centralised Procedure to all new drug substances in predefined indications will obviously increase the number of centralised applications significantly in the future.

In consequence, the number of applications to EMEA will significantly increase compared to the number of applications under the previous Centralised Procedure. In general terms, the scope of the Decentralised Procedure will be more and more focussed on MPs containing existing active substances and their generics as well as on immunological, herbal, homeopathic medicinal products, etc. (See scope of the procedure,MRP or DP - Table 4). The future will show how the changes in the legislation, by late 2005, will be reflected in the number and types of different authorisation applications at Community and MSs level.

To highlight the changes in the **Centralised Procedures** in Review 2005, a comparison has been made between Regulation (EEC) 2309/93 and Council Regulation (EC) 726/2004 in order to see whether improvements have been introduced into the new Regulation. This tendency may further help to stimulate the innovative industry in specific therapeutic indications, which will also fall under the mandatory scope of CP as of May 2008 in accordance with the Annex to Council Regulation (EC) 726/2004. (See Table 3)

Before the Review 2005, flexibility for the generic applicant whose reference product had been centrally authorised to decide whether to choose the CP or MRP/DP was not allowed and he had to follow the legislatively riles - the centralised system. Pursuant to the Review 2005, for the products not obligatory for the CP it is a company's decision which procedure to apply - CP or DP/MRP.

The timelines defined in the new legislation 2005 for the scientific evaluation of any MP by the CHMP remain unchanged compared to the previous situation, i.e. 210 days for the "normal" CP. Council Regulation (EC) 726/2004/EC introduced a new **"fast track procedure"**. This new **Accelerated Procedure provides 29% shorter** assessment time, i.e. a maximum of up to 150 days instead of the normal Centralised Procedure with 210 days CHMP assessment period (See Figure 4, Table 3).

The new legislative period for the "standard" CP (277 days) pursuant to Regulation (EC) 726/2004 as compared to the "standard" CP (300 days and over) in Regulation (EEC) 2309/93) offers also great potential for a faster placing on the market of MPs, which is of major interest from the point of view of public health.

Now, pursuant to Article 10 (3) of Regulation (EC) 726/2004, the time for Commission Decision (CD) is absolutely fixed (15 days) in contrast to the previous legislation, where that period of time was not limited and legislatively fixed. Even shortening of the approval procedure by a few days could bring significant benefit for the population and particularly from the viewpoint of "therapeutic innovation".

The accelerated approval according to Review 2005 provides the option to reduce the total approval time to 7.2 months (up to 217 days, see Fig. 4). Nevertheless, drugs accepted for review under accelerated approval legally have an effective period for evaluation of five months (150 days) after the submission. These times do not include the clock-stops caused by requests for clarification or critical missing data in the dossier. To get the best benefit out of this new procedure, there are opinions that the designation for accelerated assessment could be connected to a temporary marketing authorisation within the Centralised Procedure, Article 3 (4) of Draft Commission Regulation for Conditional MA. (62) That could be a great advantage from the point of view of public health due to receiving a temporary MA based on incomplete dossier and parallel to the benefit of going through the accelerated procedure.

However, in the interest of public health, accelerated assessment should not only refer to shorter assessment periods but should also include an abbreviated premarketing development phase for the designated MPs. Till now, there was no European equivalent of the regulatory mechanism that has been shown to be effective in the US: expedited development, accelerated approval, priori-

ty review, and rolling submission.

A comparison has been made between 35 products authorised in the US (by FDA) for the period 1998-2004 and in the EU (by EMEA) during 1995-2003. The mean total approval time (from submission to authorisation) in the EU was 12.7 (median 12.6 months) compared to a mean of 7.1 months in the US (median 5.9 months); thus, faster approval was achieved. (89)

The new EU provision for accelerated assessment could provide similar results in the future shortening the median approval time of MP as the experience with the FDA in the USA. On the other hand, the importance of preventing access of inadequately tested and assessed medicinal products to the market needs to be stressed.

At this stage, there remains an open question about the difference between the terms **"interest of patient…at Community level"** as outlined in Article 3 (1) (b), Council Regulation (EC) 726/2004) and **"major interest from the point of view of public health"** (Article 14 (9) of Council Regulation (EC) 726/2004). The need to clarify this question is further highlighted by the use of the term **"Community interest"** in Article 31, Directive 2001/83 as amended, which does not relate to the Accelerated procedure but to arbitration procedures and which also has no published interpretation. Given the use of these rather similar terms in different contexts and legal documents, it will be of utmost importance how the various EMEA experts in the Committees and Working Parties will define the criteria for an MP to comply with the concept of accelerated assessment until relevant guidelines and definitions will be available. In the first category, in Article 3 (1) (b), the interest is more on an individual level and it is related to the interest of the patient whereas in the second option, in Article 14 (9), the interest is on a broad level, which reflects the individual patient or patient groups. For all these legislative issues different interpretations could also be possible between the regulatory authorities in respect of local country morbidity, patients, health workers behaviour, and the competent expert interpretation, as well. For the 27 different MSs with various health statuses it will be a great challenge to reach a consensus on the meaning and understanding of the issues mentioned above without official explanation or published documents. The guideline on the accelerated assessment EMEA/419127/05 provides answers to these questions. (23)

The centralised approval system (normally, 277 days) without clock stop and the 217 days for Accelerated Procedure offer quicker access to the whole EU market than MRP, 420 days. As the most advantageous procedure will be DP (240 days), which in theory offers a 16% shorter period than the normal or standard CP period for those products where CP is not mandatory. For receiving a MA in more than one EU MS and when the CP is not mandatory, the DP can be a very efficient procedure. (Figure 4)

The choice of the procedure is of crucial importance for selling and marketing of the medicinal product after MAs. It should be noted, however, that industry associations continuously complain about MS not meeting their timelines in issuing national MA in the MRP/DCP. The fact that the CP involves a single procedure and up to now offered a ten-year period of protection against abridged applications also has to be regarded as an important advantage. For the Centralised Procedure, a company should submit one application (in English language) to EMEA, with only few MSs requesting the entire documentation. (11,46)

In contrast, in the existing Mutual Recognition Procedure the application should be submitted to all chosen national competent authorities of the CMSs. The same model applies to the new Decentralised Procedure where the number of dossiers will depend on the number of CMS together with RMS. In addition, some MSs require the application to be filled in their national language, thus making the procedure inflexible and much more complicated.

The Centralised Procedure provides easier maintenance in the post-authorisation phase with a single application of the MAH to the EMEA, while - in contrast - in the MRP the maintenance of the MA should be handled through the RMS to each CMSs involved in the approval procedure.

In the Review 2005, several specific situations are described where, due to the nature of a MP or the indication, an application for MA may be acceptable although the dossier itself does not yet fully comply with the requirements as outlined in Directive 2003/63/EC. The procedures for a marketing authorisation under exceptional circumstances, the assessment for conditional authorisation, the compassionate use procedure, and orphan drug designation define criteria for these situations. (28)

According to the Review 2005, orphan medicinal products should be authorised only under the Centralised Procedure (Annex (4) of Regulation (EC) 726/2004). Due to the lack of products for patients with rare diseases, orphan medicinal products will often be granted a marketing authorisation “under exceptional circumstances” and will thus be subject to annual reassessment and certain specific obligations (Article 14(8) of Regulation 726/2004). (11)

According to the new pharmaceutical legislation, MPs with an orphan designation could apply for a Conditional Authorisation. Applications under the Centralised Procedure may also take the Accelerated Procedure and receive the assessment of CHMP within 150 days and Commission decision within 217 days, when the orphan is classified in respect of “major interest from point of view of public health”, Article 2 (2) of the Commission Regulation (EC) No 507/2006 of 29 March 2006 on the Conditional Marketing Authorisations. (66)

MPs containing a designated orphan substance, which have been approved via a national or mutual recognition procedure (MRP) before 20

November 2005, cannot continue to obtain further national marketing authorisations via a MRP or a repeat-use MRP and must be resubmitted via the Centralised Procedure. Any applicant, in both situations, must contact the national competent authority concerned and the EMEA (Doc. Ref. EMEA/243280/2005 Practical Consideration). (53)

It will be very difficult for small and medium-sized enterprises (SMEs) and companies with a small selected number of EU MSs to follow the Centralised Procedure and to pay the EMEA orphan application fee, regardless of all reductions and preferences introduced. According to Commission Regulation (EC) No 2049/2005 of 15th December 2005, small and medium enterprises have also an increased opportunity to work with different specialised expert groups, working parties, scientific committees and the possibility to even use experts from outside the EU, providing certain guarantees for intensive work in the scientific approaches and reductions of fee payment. (90,91,62)

It is the intention that new and innovative medicines can be marketed easier to the benefit of the patient. All incentive for SMEs respond to the need of paying special attention to small businesses, which often lack regulatory resources and financial stability to cope with the regular EU pharmaceutical legislation and, therefore, such special provisions were introduced in order to motivate their scientific, financial and regulatory work. If most of the orphan drug companies could not be able to maintain all EU MS markets, it should be reconsidered whether the legislative switch of orphan MPs, falling under the mandatory scope of the CP, will really be beneficial and more effective than the previous option between MRP and CP.

Regarding **"compassionate use"** of medicinal products for human use, the EMEA adopted a guideline EMEA/27170/06 and Questions and Answers to patients EMEA/CHMP/ 72144/06 shall be put into practice and to be applied by every Member State. Guideline on compassionate use in the European Community pursuant to Article 83 and the Annex of Regulation (EC) No 726/2004 should have implemented legislative rules regarding "compassionate use**"** for products, which could have only a national patient application. (23,64,65)

Within the EU, the regulatory supervision of compassionate use is within the responsibility of the national health regulatory authorities. The Czech Republic, Denmark, Finland, France, Greece, Latvia, Luxemburg, and Malta have both a version for cohort programmes or individual patients. Only the individual patient basis is available in the other MSs. (92)

Some countries, e.g. Spain and Hungary, have developed compassionate use principles already many years before the Review. In Spain, law 25/1990 and Real Decreto 561/1993 established provisions for exceptional treatment of products in the clinical trial phase of research for patients not included in a clin-

ical trial. In particular, Real Decreto 223/2004, of 6th of February, has set out the definition and the new requirements. The Spanish definition is much more extended to proprietary medicinal products "for indication or condition of use different from those authorised", which is very common in the real practice. Every year, the regulatory authorities in Hungary receive about 15,000 "compassionate use" applications from patients suffering from fatal diseases wanting to import medicines that are not placed on the Hungarian market or when the MP is already authorised but its price and reimbursement conditions have not been published. Medical specialists with adequate qualification may also initiate the individual import procedure for such products. Generally speaking, the drug in question must be authorised in the country from which it is to be imported. (93,94)

This disharmonisation between the MSs in both options relating to "compassionate use" and "named and cohort programmes" should have been solved with the new EU legislation that came into force in late 2005. Article 83, Council Regulation (EC) 726/2004, only describes the options "subject to an application for a marketing authorisation" or "undergoing clinical trials". The compassionate use of an investigational medicinal product (IMP) is only for a "group of patient directed". The Council Regulation will allow compassionate use for products provided for cohort programmes, which serve a large number of patients. Besides compassionate use programmes, the individual patient may be able to access unlicensed medicines through clinical programmes, prescription, or importation based on Directive 2004/27/EC, Article 5. While Council Regulation 726/2004 focuses only on cohort studies, Directive 2004/27/EC allows physicians to request unauthorised MP for individual patient under their own responsibilities. (31)

The EudraCT database set up according to Article 57 (n) of Regulation (EC) 726/2004 will include information on clinical trials being conducted in the EU. From this database it will be possible to identify the status of a specific MP. EudraCT will therefore be valuable to estimate whether a MP can be assigned a compassionate use status or not. In most countries the current system allows flexible and rapid access to unapproved MPs through the compassionate use procedure. (11)

Future experience will show whether the new harmonisation process, introduced by the review, relative to "compassionate use" will increase the flexibility and reduce bureaucracy compared to the current situation in MSs. At present, the EMEA guideline CHMP/5579/04 is still under development and it will obviously provide answers to some of these questions. (23)

Article 14 (8) of Regulation 726/2004 introduces the concept of a MA under exceptional circumstances. The guideline EMEA/357981/2005, in conjunction with guideline EMEA/CHMP/96268/2005, covers different post-

approval activities and intervention measures designed to proactively identify, prevent, and decrease the risk inherent for such medicinal products. (69,95)

Clarification is still needed concerning different aspects of MA under exceptional circumstances and conditional MA. The guideline for exceptional circumstances EMEA/357981/2005 attempts to define the differences between the two procedures for marketing authorisation under Exceptional Circumstances and Conditional Approval of medicinal products. Where the comprehensive data, in line with the Directive 2003/63/EC, Part II (6), cannot be provided at next steps, the MP will be approved under MA for exceptional circumstances. (28,69)

In contrast, a MP for which the applicant could demonstrate a positive benefit/risk balance based on early evidence of effect that is expected to predict clinical results from scientific knowledge or comprehensive information may be authorised under Article 14 (7) of Regulation (EC) 726/2004 (MA under Conditional Circumstances). This temporary authorisation is not indented to remain conditional, upon the yearly renewal, once the required data for the evaluation of the benefit/risk ratio is provided, the MA may become a normal authorisation. A Conditional Marketing Authorisation could be granted in the absence of comprehensive clinical data when it is likely that the applicant will be in a position to provide such data in a short timeframe according to Article 4 of the Commission Regulation for Conditional marketing authorisation. Further EMEA guidance (EMEA/50995/2006) will provide answers to many questions. (23,66,67)

Such fine distinction should be made between the approval under Conditional Marketing Authorisation and MA under Exceptional Circumstances. When the applicant will be in a position to provide the missing clinical data in a short timeframe, exceptional circumstances will not be appropriate and the temporary authorisation could be a choice of decision. The problem is that the terms “rare indication” or “ethical principles” in Directive 2003/63/EC, Part II, (6), need more clarification in order to avoid any interpretation by the CHMP between both above mentioned procedures for MA. Even though some principles for the “rarity of the indication” and “medical ethics” are presented in the EMEA guideline concerning exceptional circumstances, (EMEA/357981/2005). The EMEA opinion for the MP in question could be taken in both directions: either as a Conditional Marketing Authorisation or an authorisation under Exceptional Circumstances. The MA under Exceptional Circumstances will be more convenient for the applicant when he is unable to provide comprehensive non-clinical or clinical data on the efficacy under normal condition of use and a listing of the non-clinical or clinical efficacy or safety data cannot be comprehensively provided. (69)

In the established Decentralised Procedure the applicant is again free

to choose the EU Member State that will act as the Reference Member State (RMS). In the past, concerning the MRP, the applicant considered such factors as the processing time taken by each national authority, the authority's reputation and willingness to co-operate. The applicant was even recommended to discuss the proposed application with the RMS. Furthermore, this procedure adjunct had offered the possibility of selecting only the Member States where a positive evaluation of the MP could be expected in the first step. (75,96)

In a second step, the so-called "second wave", a further MRP/DP could be initiated with additional MSs. However, if the danger of rejection by one MS was still perceived, the applicant should precisely assess the MP with respect to the "potential serious risk to public health". The criteria in the draft Guideline for the "risk to public health" are now established and, therefore, all strategies associated with this issue should be very carefully considered to avoid eventual arbitration. According to the legislation, Directive 2001/83/EC, Article 18, a medicinal product, which has already received a MA in one MS, should follow the MRP. Otherwise, for a MAH in more than one MS without a previous national authorisation, Article 28 (3), the Decentralised Procedure will be mandatory. This will help to avoid duplication of work associated applications, payments, and the time for the National Authorisation and after that for the Mutual Recognition Procedure, so far through the Decentralised Procedure the applicant could save the work and the time during the National Authorisation.

A company's marketing strategy and/or financial perspective could decide upon the RMS and the CMSs of the DP/MRP for generics, for which the reference medicinal product has been authorised via the Centralised Procedure. For middle-size pharmaceutical companies, which intend to start marketing in a restricted number of MSs, the expenses for authorisation fees could be much lower than via the Centralised Procedure. According to the new legislation for the DP/MRP, summaries of product characteristics (SmPCs) and labelling are now part of the approval process; previously, these were issues to be solved after the Assessment Report. That means that harmonisation in both procedures, DP/MRP, concerning SmPC and PIL will be performed between all MSs parallel with the Assessment Report.

According to the previous MRP procedure established in 1998, in case of CMS(s) disagreeing with the RMS assessment report the applicant had been able to withdraw the application from those CMS stating objections. The MP could be marketed in the remaining MSs after receiving the respective marketing authorisation. If the application had not been withdrawn and MSs had failed to reach an agreement, the procedure had to follow the Community referral described in Article 29 of Directive 83/2001/EC. (19)

Today, in case of objections by any MS with regard to a possible risk to public health, a withdrawal after availability of the assessment report is no

longer possible; the procedure will be transferred to the CMD (h) Group for clarification and, if this cannot be reached with consensus, will have to follow the arbitration procedure. Obviously, the repeal of the possibility to withdraw an application will result in an increase of arbitration cases. At the same time, however, this process will help to clarify the future definition of "risk to public health" and will harmonise MS positions.

Now, the Decentralised System (DP) has advantages to the previous MRP (420 days) not only with respect to the shorter period with 180 (42%) days in the RMS and CMSs phase but also in the arbitration process, due to the efforts of the CMD (h) Group in case of reaching consensus in 60 days (270). It is possible to end the procedure at Day 105 if consensus is reached, at Day 120, at Day 150 and at Day 210 (followed in each case by 30 days for the national step - text translation/granting of marketing authoriation). (97)

The new updated MRP, where claims "potential serious risk to public health" are raised, also profits in the same way from the new activity of the established CMD (h) group.

A very important step in the harmonisation process of the marketing authorisation procedures is the harmonisation of the arbitration process. In case of arbitration, the Commission's powers to implement the CHMP's opinions are expanded by Review 2005. The new article makes arbitration obligatory if the MSs cannot resolve differences arising from the MRP/DP. The proposal of the European Commission for a "Guideline on the definition of the potential serious risk to public health" of February 2005 has made the process clearer for the different MSs by pointing out such potential threats for the community. The guideline, which has been under discussion for nearly a year and published in June 2006, is intended to address the problem that arises when one MS refuses to recognize a MA granted by another MS. (72)

The informal Mutual Recognition Facilitating Group (MRFG) had been established by the Member states in March 1995 to improve the operation of the Mutual Recognition Procedure and the work in the SmPC harmonisation field. The Member states recognised that there needed to be a group that could coordinate and facilitate the operation of the decentralised MRP. The Group had no formal position in EC legislation but has established itself as a major player in the new European system. The Group provided a forum where procedural and regulatory issues can be discussed and problems resolved and a series of procedural documents have also been agreed upon and the Group has played a major role in the ongoing work on the Notice to the Applicants. This system allows the MS to follow the progress of individual applications and their subsequent variations. As intended, the Mutual Recognition Procedure has been established as the major route for the licensing of medicinal products through the new European single system. (98)

MRFG's successor with a legal mandate, the CMD (h), offers a potential to avoid arbitration procedures by an additional clarification/discussion step that only takes 60 days. Only in case the CMD (h) will not reach consensus, the procedure will be referred to CHMP for arbitration. All concerned MSs should accept the decision for the MP in question. Although the MRFG's functions were primarily regulatory and procedural, the CMD (h) is also requested to give scientific opinion. CMD(h) plays a leading role in accelerated solving the problems arisen in the decentralised system, including discussions at CMD (h) in the Assessment step II in the DP, whenever needed. (31,74,99)

How such consensus is reached between the members of the CMD group is a serious scientific and political challenge, where different attitudes/influences should be taken into consideration within only 60 days.

"Co-Marketing" (second application with the same International Non-proprietary Name (INN) but different trade name and the same or different MAH) has already been an option for the decentralised system. For medicinal products authorised via CP where companies wished to market the same MP under more than one trade/invented name, additional applications for separate authorisation has to be submitted. Pursuant to Article 82 (1), Regulation (EC) 726/2004, the European Commission has to be informed in advance and it shall authorise if there are "objective verifiable reasons relating to public health regarding the availability of medicinal products to health care professionals and/or patients, or for co-marketing reasons". In order to use the possibility of Co-Marketing, a comparatively simple double application can be certified by the competent authorities for Co-Marketing in the context of the CP and MRP/DP. (11)

Actually, the possibility for Co-Marketing in the new legislation 2005 for the CP is intended for better covering the EU market in order to provide better availability of MP for public health reasons.

The Review 2005 introduced many advantages for generic medicinal products, which allow generics to reach the Community market faster. Directive 2001/83/EC on the Community Code relating to medicinal products for human use, Council Regulation 2309/93 and Community marketing authorisation procedures (98/C 229/03) have defined an **abridged application,** which could be lodged only with the authority that have evaluated and authorised the original product as this authority is holding the dossier of the medicinal product, which is essentially similar to the second application. (31,43,100)

The general principles for generic applications have not been changed in the last Review from 2005. The legal basis for the submission of abridged application is laid down in Art. 10 (1) of Directive 2004/27/EC. The applicant is not required to provide results of pharmacological and toxicological tests or results of clinical trials, the documentation and data required can refer to information

that is contained in the dossier of another "original" authorisation. Generic applications typically include chemical-pharmaceutical data and the results of bioequivalence studies, which demonstrate the quality and the "essential similarity" of the product. For information concerning the safety and efficacy of the active moiety, the regulatory agencies refer to the data that have been established in the reference product's application for authorisation. A number of new guidelines for the authorisation of generics in the Centralised and Decentralised Procedure have been developed in order to facilitate their market access. (30,31)

In the previous legislation, generics were only authorised in the MS where the reference medicinal product had been authorised. In case of a RMP not being marketed or having been withdrawn from a MS, the generic medicinal product could not be placed there either. Following the changes introduced by the Review 2005, many generics will appear in different MS where the reference innovative medicines has never been marketed. Apparently, that situation depends on the pharmaceutical market of the MS, especially where the MAH was not motivated to authorise an innovative MP in that country.

The changes focussed on the reference medicinal product, the non-availability of which in a specific MS will not be an obstacle for a generic MA any longer. However, different challenges could arise on the part of the MS where the innovative MP had not been authorised. This new concept of the RMP is a very important, positive step especially for the new Member States where many of the innovator products have never been authorised or the marketing authorisation for many reasons has expired without a renewal or without having been withdrawn. In many EU countries the generic industry will benefit from this new provision as this concept will stop the lack of a reference product blocking the development of generics for these markets and, consequently, many patients will be able to benefit from a treatment that they have not had access to before.

Directive 2001/83/EC as amended, requires the MS responsible for the MA of the reference MP to provide information to other MS on request. The generic applicant can use different ways for collecting such information without being sure for the real availability of the provided data. The various homepages of the competent authorities in the EU provide complex differences and language difficulties for receiving reliable information on the reference product or the access to the authorised medicinal products is permitted only against payment. (30)

The challenge for the generic industry will be to find out and indicate where the reference medicinal product has been authorised for the first time. Nevertheless, the established Community Register on centrally authorised products and the MRI provide information for 9831 products (access on 29. Nov.07) on MRP but the substantial rest of the authorised reference medicinal products

are not presented in a single EU database. (36,45a,101)

Because of the lack of such official EU database, which for the US market is readily available, only the chronology in the MA of the innovative medicinal product could help to find out the searched information. Any co-marketing authorisations granted could provide additional complications in receiving the correct information. Thus, it will be a great challenge for the generic industry to find out the objective information. In Europe, competent authorities have never considered it appropriate to address patent issue within the context of MA for MP. However, this could be achieved with the establishment of a European equivalent of the US "Orange Book", a register including patent and marketing authorisation information for medicinal products.

Directive 2001/83/EC does not provide any measures for supervision or sanctions in case the competent authority which has authorised the reference medicinal product does not provide the required information in the appropriate period of time. In addition, it cannot be judged yet if the "one-month" period will be enough for providing the relevant information where the product documentation is only available in a national language, which is not helpful for the authority awaiting this information. In this context, the working documents on the minimum information to be provided to the competent authority, established by the CMD, is a step forward. (29)

With the changes in Article 10 (2) (b) 2004/27/EC a clear definition for a "generic products" is provided, where "the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form". It is clearly the intention to prevent generic products being blocked by the innovator making changes to the active substance and thus gaining an extended protection period. (13)

The update of the legislation from 2005 aims at shortening the assessment period of generic products and preventing the innovative industry to involve any law steps in order to prolong the marketing protection of the MP on the pharmaceutical market in the region. Although the Directive includes a definition for a "reference product", there is no legislative distinction between **"original"** and **"reference product".** Variations of summary of products characteristics (SmPCs) and disharmonisation between the "original" and the "reference products" from country to country are probably possible for non-centrally authorised MP. Both could be absolutely identical and the reference product could be the original one but it is not explicitly mentioned in the pharmaceutical legislation. The important step is that the Member State where the application is submitted shall request the competent authority of the other Member State (where the reference product is already authorised) to transmit a confirmation within a period of one month: Article 10 (1), Directive 2004/27/EC. (13)

Another open question is how a biosimilar medicinal product which, by

definition, will have to be applied for via the Centralised Procedure, will refer to a reference medicinal product authorised before establishing the European Agency in 1995. Does this, in consequence, mean that such biosimilars applied for to the EMEA, where the reference product has been authorised before the establishment of EMEA, will in fact be classified by EMEA as a new full application if the RMP has not undergone the Centralised Procedure? One of the greatest hurdles is that the originator's data often remain inaccessible for cross-reference by a second applicant because most recombinant products have been submitted via the earlier concertation procedure or by National Procedures for MA. (33)

At present, the beginning and the end of the period of **data protection** for the respective reference product is of great importance for the selection of RMS and CMSs. With the MRP and DP, the period of protection already begins with the first MA in the respective MS. Normally, the RMS would be the country with the largest market for the MP, which offers a ten-year period of protection after valid authorisation. The data protection period in the CMSs of second or another "wave application" shall be respected by the generic industry as that period will be shorter than the 10 years in the RMS.

With the Centralised Procedure, the period of data protection starts from the date of the MA, i.e. at the same time for all countries and markets; currently, this is 10 years. With the European Union Review 2005, the periods of protection are adapted to both European Union procedures of admission.

In accordance with MRP/DP, authorised MPs will be granted a further one year period of protection of the data if a change of the classification of the medicine, i.e. an "OTC switch" of the prescribing to OTC status, has been approved due to important pre-clinical and clinical examinations. Within this one year the authority will not evaluate requests of other applicants for conversion of the supply status, which refers to the first application. With the Centralised Procedure, such a procedure is not intended to be applied due to the nature of the MP - "over the counter" (OTC) authorised under the Centralised Procedure and, also, such a "switch" is less intended. (31,102,103)

The additional year of data protection, an incentive provided for a *new indication with "significant benefit in comparison with the existing therapies"* will motivate the industry to place such a product on the market. On the other hand, the new indication will not be covered with additional ten years marketing protection, which will be in favour for the generic industry and the patient as well.

After the implementation of the "Bolar" provision into national legislation, the required development activities can be performed in the EU. This new provision may help to minimise the conduct of clinical trials by the generic industry outside the EU during the period of data exclusivity. The

absence of such a provision in the previous legislation had the consequence that the relevant trials took place outside the EU. The context of such enlargement was that some of the new Member States had this clause in their legislation. Finally, to counterbalance the practical impact of the extension of data protection in certain MSs the new legislation introduced the opportunity of clinical trials necessary for the application for a generic marketing authorisation being conducted while the reference product is still completely protected by a patent. Initially, the Commission did not accept this claim but finally joined the declaration of the Council in order to bring balance between innovative and generic products. Only the export provision was not accepted and the final text states: "Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3, 4 and the consequential practical requirements shall not be regarded as contrary to patent right or to supplementary protection certificates for medicinal products". (44)

In real life, at least part of the two years of earlier generic submission before expiration of the marketing protection of the reference product will be used for the evaluation of the submitted generic dossier. However, this will still give the opportunity for an accelerated launch of generics. In general, the legislative changes and amendments to the data protection period which have been in force since late 2005 provide a significant step forward for reaching rapid access to market and to the patient as well.

However, the **Transitional Law on Data Exclusivity** (Directive 2001/83/EC, Article 2) will apply only to such MPs which have been authorised after the entry into force of the new European Union legislation. Thus, the currently still existing advantages of the Centralised Procedure of the use of the periods of data protection and the marketing protection thereby will be reduced and harmonised within all EU countries in the future and many new generics will come easier and sooner to the EU market. However, since the new periods of protection will only apply for such reference products, which have been authorised after November 2005, in accordance with the formula "8+2+1" the first generic requests according to the new timelines could only be submitted at the end of 2013. (31)

Together, the absence of an obligation for the reference medicinal product to be on the market, the possibility to waive the requirements of bioavailability studies of the generic medicinal product when it meets the relevant criteria as defined in the appropriate detailed guidelines and the Bolar provision are in favour of the generic industry for shorter and accelerated market access of its MPs (See Table 2). (31, 43, 44)

Commencing trials before patent expiry will give the generic industry the opportunity to prepare and submit the MP dossier much earlier. This may help to save cost and time as the generic product could be placed on the market

immediately after patent referent product expire. In the previous legislation, before 2005, the generic dossier submission was possible after the end of data protection.

Even though the amendments in the review of the pharmaceutical legislation 2005 provide many advantages for the generic industry for faster access to the market, some critical legal issues are still left open. One of them is the lack of a clear statute for the availability of single EU official information relating to data exclusivity periods and patent issues of the reference medicinal products. All this information is available only on a MS level.

The harmonisation and shortening of data exclusivity periods in combination with an additional exclusivity period for significant new indications will motivate the innovative industry to develop new medicines and new indications, which is one of the major aims of the amended European pharmaceutical legislation in 2004.

The simplified procedure for herbal medicines introduces a new category of herbal medicines based on traditional use for which safety and quality have to be shown like for other MP.

The legal basis for submitting a marketing authorisation application for homeopathics and herbal medicinal products (HMP) is Directive 2001/83/EC. Directive 2004/24/EC amends Directive 2001/83/EC to cover traditional herbal medicinal products. This directive has been issued with respect to the operation of the new legislation and is providing a harmonised legislative framework for authorising the marketing of traditional herbal medicinal products based on a Simplified Registration Procedure, which is known as "traditional-use registration". Traditional use for 30 years should be demonstrated including at least 15 years in the Community. Thus, herbal MP from outside the EU may also obtain traditional herbal status. (31)

The provisions of Directive 2001/83/EC only relate to products which are classified as medicines and many herbal remedies will be able to continue to be sold in other categories, e.g. as a food or cosmetics in accordance with the national legislation. Herbal medicinal products which can be given a marketing authorisation on the basis of supporting safety and efficacy data, e.g. using published literature, will not be eligible for the **Simplified Registration Procedure**. Likewise, homeopathic medicines will be excluded.

The Mutual Recognition Procedure was introduced for homeopathic and herbal medicinal products with the possibility to include more than one Member State in the simplified procedure. The parallel **Simplified Registration Procedure** will lead to quicker parallel market access for homeopathics and herbal medicinal products, which was not possible till the change in Review 2005. On the other hand, the provision in Directive 2004/27/EC will provide an opportunity for EU harmonisation of the procedure relative to herbal and home-

opathic medicinal products and Member States should take into account MAs that have been granted in other MSs when evaluating an application. (13)

The new EMEA Herbal Medicinal Product Committee is a key element in the new regulatory environment for herbal products in the EU and it may provide major clarifications from regulatory point of view through the establishment of monographs and lists for HMP. Of particular importance for the future assessment of the HMP is the establishment of the Committee on Herbal Medicinal Products (HMPC) within EMEA, which supports the work of Committee for Human Medicinal Products. The Committee has enlarged responsibilities within the Community law. At the beginning, the original proposal was giving to this Committee very limited responsibility; the published text defined a much wider scope including in particular the final judgement in an arbitration process in cases where mutual recognition procedure between the EU MSs could not be finalized successfully. The HMPC gives confidence to the manufacturers in the area to submit applications. (104)

The transitional period for herbal medicinal products till 2011 is also an opportunity to allow products existing on the market to continue to accumulate evidence of usage in the EU. Overall, by 2011 all herbal medicinal products will have to be licensed/registered in order to stay on the market. This allows sufficient time for regulators/companies to adapt themselves to the new requirements relating to traditional herbal medicinal products. Pharmacovigilance requirements such as variations (e.g. to keep the quality section up-to-date), renewals, and pharmacovigilance apply in the same way as for non-herbal medicinal products and should be taken into consideration by the drug regulatory authorities in the different MSs. (13)

Directive 2004/24/EC requires the Commission to prepare a report by 30 April 2007 detailing an assessment as to whether the Simplified Registration Procedure should be extended to cover some categories of non-herbal traditional medicines. Points to consider in the report with respect to classification, labelling, and advertising are the same as those applied to non-herbal medicinal products.

5. Outlook and Conclusion

Main challenges for accelerated market access of MP in Review 2005

The pharmaceutical review in 2005 was designed to yield concrete benefits for European consumers and patients in the rapidly changing medical science. The Review focuses on reinforcing the proven success of the EMEA set up in 1995. Important attempts are focused on optimising, rationalising and shortening the current regulatory processes without changing the principle of the existing centralised and decentralised structures.

The main challenges for the EMEA and NCAs over the next few years will be their ability to meet the increasing expectations of all parties involved. The new legislation is focused on accelerating all procedures for MA and gave special attention to small and medium sized enterprises. The new legislation from 2005 provides for specific measures aiming at reducing the time for the MA procedures and the cost for such enterprises

Some major challenges could be summarised as follows:

Success in the intellectual property

- Data protection periods are being harmonised with the period provided for the centrally authorised MP**:** eight years data exclusivity and ten years marketing protection.
- The terms “generic medicinal product”, “reference medicinal product” and ‘biosimilar” are introduced and defined in the legislation.
- The possibility to prepare and file a generic application during the validity of data exclusivity not contrary to the patent right including the supplementary protection certificate applied to the reference medicinal product is being introduced.
- An extension of one year of the data protection period can be allowed if a medicinal product, covered by the normal data protection period, has developed a new therapeutic indication with an important benefit for the patients, “significant indication”.
- The reality is that the generic industry will profit from the “eight-year provision” not earlier than 2013.

Success in the Centralised Procedure

- The changes of the CP include opening of the procedure to more types of new medicines, which will be available at the same time for all patient in the EU, provided the MAH decides to market the product in all MS.

- MPs with an orphan designation now fall under the mandatory scope of the CP with the main idea that all EU patients who need them should benefit.
- Concerning the duration of the assessment in the **Centralised Procedure**, the current deadline of 210 days could be reduced to 150 days (by 29%) in case of using the Accelerated Procedure for products of significant therapeutic interest.
- The Community Decision time is decreased by 36 days by the Review 2005 compared to the old legislation.
- The time for the Community Decision has been fixed to 15 days, which was not explicitly fixed in the previous EU legislation.
- Different specific types of temporary marketing authorisation procedures have been introduced, e.g. Compassionate use; Conditional Authorisation for MP
- Orphan MP could be qualified for an Accelerated Procedure with a 217 days timeline.

Success in the Decentralised system of MA

- The decentralised system is facilitated by introducing different modalities: the new Decentralised Procedure with 240 days is designed to be 180 days (42%) shorter than the MRP (420 days), depending on whether or not the medicinal product is already authorised in a MS. When the DP ends at 105 Day, it could be finished earlier in 150 days, or 180 days, which in fact is 270 days (64%), or 240 days (57%) shorter than the MRP respectively.
- A guideline on the concept of "Potential serious risk for public health" has been published in order to clarify the MSs public health objection.
- The CMD (h), successor to the previous informal MRFG, has been introduced with a legislative status. One of the objectives of CMD (h) is to avoid and facilitate arbitration procedures in the MRP/DP.
- Medicinal products not authorised or with pending authorisation could be placed on the market for justified health reasons if possessing authorisation in another MS (national legislative provisions need to be developed).

Success in the arbitration system of MA

- The CHMP time is by 30 (50%) days shorter.
- The Commission decision referral time is decreased by 38 (42%) (from 90 to 52 days) by the Review 2005 compared to the previous legislation.

- The referral procedure is in general by 68 (38%) days shorter (from 180 days to 112 days) than in the previous legislation.

Success in Herbal and Homeopathic MA

- **Simplified Registration Procedure** for certain homeopathic and traditional medicinal products is established. Overall, by 2011 all herbal medicinal products will have to be licensed/registered in order to stay on the market.
- Simplified registrations of homeopathic and traditional MPs granted by one Member State should be recognised throughout the Community and MRP could be applied.

Thanks to the four co-existing EU marketing authorisation procedures: national, mutual recognition, decentralised and centralised procedures, and the different specific, temporary, or accelerated procedures the patient in the enlarged EU with 27 countries is apparently assured with the needed medicinal products. Nevertheless, the implementation of all new and updated approval procedures for MPs are connected with many challenges and long term evolution.

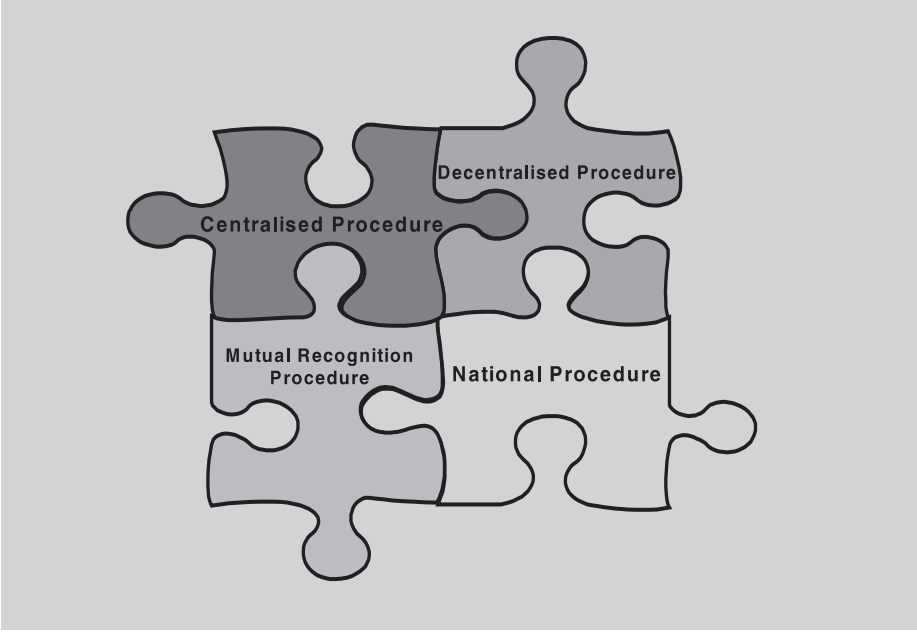

Figure 7. Marketing authorisations procedures in the EU

The various marketing authorisations (See Fig. 7) are tools of choice for the applicant, except in the mandatory cases, and they add up to each other like a puzzle built up by the innovative and generic industry in order to cover the EU market with all necessary, safe, qualified and effective medicines.

In the EMEA Road Map to 2010, the current challenges to be faced in the pharmaceutical field are summarised, e.g. limited available resources, duplication of work, increase of efficiency of operation, further coordination to ensure a harmonised approach in the field of scientific advice, communication and outcome measurement. Over the years, the EU regulatory system will be confronted with significant changes in the legislative impact of the new Community legislation and institutional impact of the enlargement of the EU nature. In addition to these significant challenges, other developing factors, which are nonetheless important, will have to be taken into account such as a potential continuation of the EU enlargement with other countries such as Turkey also seeking membership.

The European Medicines Agency will have to find the right balance in terms of the expectations for the timely delivery of science based opinions, increased involvement in the protection and promotion of public health, regulatory consistency, transparency, better information, and earlier communication. The continuation and adaptation of the Agency's networking model will also require that national competent authorities (NCAs) are able to respond adequately to the changing regulatory and administrative environment. The NCAs should contribute to the future system more and more since this will be a key for the overall success in the EU-pharmaceutical field.

A complimentary document to the EMEA Roadmap has been drafted by the Heads of Medicines Agencies (HMA) describing the challenges and goals from the MS network perspective. This HMA Strategy Paper has been widely consulted with stakeholders and is published on the HMA website. (24,30)

References

1. Die **Entstehung und Entwicklung der Europäische Union**. Taschen Atlas Europäische Union, Klett-Perthes Verlag., ISBN 3-623-00022-1. 2004.

2. **Treaty establishing the European Economic Community, 1957.** http://europa.eu.int/eur-lex/lex/en/treaties/treaties_founding.htm

3. **Treaty of Amsterdam amending** the Treaty on European Union, the treaties establishing the European communities and related act. *Official Journal* C 340 of 10 November, 1997.

4. **Lisman J,** ae all. Introduction to EU Pharmaceutical Law, *RAJ. Pharma*, Jan. 2005, p. 23-27.

5. **Single European Act.** *Official Journal* L 169 of 29 June 1986. http://europa.eu.int/eurlex/lex/en/treaties/treaties_other.htm

6. **Treaty establishing the European Community.** *Official* Journal L 224 of 31 August 1987*Official Journal* C 224 of 31 August 1992*; Official Journal* C 340 of 10 November 1999; Official Journal C 325 of 24 December 2002. http://europa.eu.int/eurlex/lex/en/treaties/treaties_founding.htm

7. **Treaty establishing a Constitution for Europe.** *Official Journal* L 310 of 16 December 2004. http://europa.eu.int/eur-lex/lex/en/treaties/index.htm

8. **Valverde J. L.** Pharmaceutical and health policy in the content of the new EU Treaty. The challenge in the new Pharmaceutical legislation. Pharmaceutical Policy and Law. Volume 6, ISBN 158603521 5 (IOS Press).2005.

9. **Council Directive 65/65** on 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal product. *Official Journal* L22 of 9 Febryary.1965, p. 3-10.

10. **Regulation No 2309/93/EWC** laying down Community Procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. *Official Journal* L 214, 24 June 1993, p.129-162. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

11. **Regulation (EC) No 726/2004** of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, *Official Journal* L 136, 30/4/2004p.1 - 33. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

12. **Council Directive 93/39/EEC** of 14 June 1993 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC in respect of medicinal products**.** *Official Journal* L 214,

24/08/1993 p. 22 – 30.

13. **Directive 2004/27/EC** of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. *Official Journal* L 136, 30/4/2004 p. 34 – 57. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

14. **Second Council Directive 75/319/EEC** of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products**.** *Official Journal* L 147, 09/06/1975 P. 13 - 22.

15. **Council Directive 87/22/EEC of 22 December 1986.** on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology *Official Journal* L 015, 17/0611987 P. 0038 - 0041.

16. **Evaluation of the operation of Community procedure for the** medicinal products", Evaluation carried out on behalf of the European Commission, Cameron McKenna – Andersen Consulting,
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2000/nov/reportmk.pdf

17. **Review of Pharmaceutical Legislation**. European Commission Discussion Document, Final Version. Brussels, 22 January, 2001.F4
http://ec.europa.eu/enterprise/pharmaceuticals/review/doc/reviewrp_en.pdf

18. **Brunet Ph**. Et all. The New pharmaceutical legislation. *Pharmaceutical Policy and Law. 6* ISBN 1 58603521 5, 2005, p. 33-45.

19. **Directive 2001/83/EC** of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use .*Official Journal* L 311, 28/11/2001 p. 67 - 128
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

20. **Directive 2004/24/EC** of the European Parliament and of the Council of 31 March 2004 amending as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use *Official Journal* L 136, 30/4/2004 p. 85 -90a.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

21. **Work Programme for the European Medicines Agency 2005**. EMEA/MB/138351/2004/en/Final. Adopted by the Management Board on 16 December. 2004 .
http://www.emea.europa.eu/pdfs/general/direct/emeawp/13835104en.pdf

22. **CHMP, January plenary meeting 2005**. EMEA/22735/2005.
http://www.emea.eu.int/pdfs/human/press/pr/2273505en.pdf

23. **EMEA Implementation of the new EU pharmaceutical Legislation.** Publication and consultation of EMEA guidance documents implementing the new pharmaceutical legislation. http://www.emea.eu.int/htms/general/direct/legislation/legislationhuman.htm

24. **The European Medicines Agency Road Map to 2010**: Preparing the Ground for the Future. EMEA/H/34163/03/Final, 4 March, 2005.
http://www.emea.europa.eu/pdfs/general/direct/directory/3416303enF.pdf

25. **Council Directive 87/21/EEC** of 22 December 1986 amending Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal. *Official Journal* L 015, 17/01/1987 p. 36 – 37.

26. **Lisman J.** An Introduction to EU Pharmaceutical Law. Published by Brookwood Booklets. ISBN 1-904255-06-X. 2005.

27. **Judgment of the Court (Fifth Chamber)** of 3 December 1998. Medicinal products - Marketing authorisation - Abridged procedure - Essentially similar products. Case C-368/96**.** European Court reports 1998 Page. 07967.

28. **Amended by Commission Directive 2003/63/EC** of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use *Official Journal* L 159, 27/6/2003 p. 46 - 94.
http://www.emea.europa.eu/pdfs/general/direct/directory/3416303enF.pdf

29. **Information to be submitted by the MS of European Reference Product** -CMD (h) Working Document **J**anuary 2006 http://www.hma.eu/

30. **Heads of Medicines Agencies**. http://www.hma.eu

31. **Consolidated Directive 2001/83/EC** of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

32. **EMEA** Guidelines on similar biological medicinal products containing biotechnology/ derived proteins as active substance **/CHMP/BWP/49348/05.** London 22 February 2006. http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf

33. **Schofiel I.** Generic biological: Where are we now? *RAJ Pharma.* July, 2005, p. 489-492.

34. **RAJ** asked six experts at the European Medicines Agency to explain the background to proposed guidelines for assessing biosimilar products. Regulating similar Biological Medicinal Products in the EU. *RAJ Pharma.* Nov, 2005, p. 787-791.

35. **Committee for proprietary medicinal products**, Summary of opinion for Omnitrop, CHMP/3184/03.London, 26 June 2003.
http://www.emea.eu.int/pdfs/human/opinion/318403en.pdf

36. **Community register of medicinal products for human use**
http://ec.europa.eu/enterprise/pharmaceuticals/register/register.htm

37. **Nick C**. Biogenerics: A new Regulatory Territory. *RAJ - Pharma*, 2004, May, p 329-333.

38. **Notice to applicants**. Volume 2A Procedures for marketing authorisation, Chapter 1, MA, November 2002, updated version November 2005. Revision 3 http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

39. **Draft-Guideline on Elements Required to support the significant clinical benefit** in comparison with existing therapies of a new therapeutic indication in order to benefit from the extended (11 years) marketing protection period. 16. 12, 2005 http://www.emea.europa.eu/htms/general/direct/legislation/legislationhuman.htm

40. **International statistical classification of diseases and related health problems**-Tenth revision 1996. World Health Organisation, Geneva, 1243

41. **Regulations 2003/1084/EC Commission Regulation (EC)** No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State *Official Journal* L 159, 27/6/2003 p. 1 - 23. http://ec.europa.eu/enterprise/pharmaceuticals/

42. **Commission Regulation (EC) No 1085/2003** of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93 *Official Journal* L 159, 27/6/2003 p. 24 – 45. http://ec.europa.eu/enterprise/pharmaceuticals/

43. **Costa M.P**. at all. EU Pharmaceutical Legislation will allow generics to reach the marker faster. *RAJ Pharma.* Mar. 2005, p 163-168.

44. **Brunet Ph**. et all. The new pharmaceutical legislation. Pharmaceutical Policy and Law 6, IOS Press, ISBN 1586035215, 2005.

45. **Electronic Orange Book**, Approved Drug Products with Therapeutic Equivalence Evaluations. http://www.fda.gov/cder/ob/default.ht

45a. Product-Information Documents
http://eudrapharm.eu/eudrapharm/searchbykeywordresult.do

46. **Lemaire O**. Why Regulators in Europe May have to pay More Attention to Patent Law. *RAJ Pharma*, May. 2005, p. 343-348.

47. **NTA -Volume 2A**, Procedures for Marketing Authorisation, Chapter 1- 7 http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm

48. **Committee for Medicinal Products for Human** Use CHMP working parties and other groups.
http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP_WPs.html

49. **Committee for Medicinal Products for Human Use**.
EMEA/CHMP/111481/2004 Rules of Procedure http://www.emea.eu.int/pdfs/human/

50. **Guideline on therapeutic areas within the mandatory scope of the CP** for evaluation for MA applications with reference to article 3 (3) of Annex Regulation (EC) No 726/2004 EMEA/28954/2005/, London, 19 October 2005.
http://www.emea.eu.int/pdfs/human/regaffair/28295405en.pdf

51. **Optional scope of the Centralised Procedure in accordance** with article 3 (2) (b) of Regulation (EC) No 726/2004. 21/12/05

52. **Accelerated evaluation** of products indicated for serious diseases life threatening or heavily disabling diseases.CPMP/495/96 rev. 1. London, 18 September 2001. http://www.emea.eu.int/pdfs/human/regaffair/049596en.pdf

53. **Practical consideration** on the impact of the pharmaceutical legislation on Marketing Authorisation Applications via the Centralised Procedure and Centrally Authorised medicinal products for Human use. EMEA/243280/2005. Rev. 2
http://www.emea.eu.int/pdfs/human/euleg/24328005en.pdf

54. **PIM** Guidance for the applicants for the centralised procedure, Draft EMEA /413933/2005 v 0.4 from 08 December 2005. http://pim.emea.europa.eu/doc/PIM%20Guidance%20for%20Applicants%20v0.4%20published.pdf

55. **Cabri P.** et all. Orphan medicinal products: A challenge from an industry point of view. Pharmaceutical Policy and law ISBN 1586 145 1 (IOS press) 3, 2001, p. 47-54.

56. **Press release**. EMEA publishes first Summaries of Opinion for designated orphan medicines. Doc. Ref: EMEA/d/7426/02. London, 21 March 2002.
http://www.emea.eu.int/pdfs/human/comp/742602en.pdf

57. **Regulation (EC) No 141/2000** of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products *Official Journal* L 18, 22/1/2000 p. 1

58. **Annual Reports of European Medicines** Agency-2000, 2006
http://www.emea.europa.eu/htms/general/direct/ar.htm

59. **COMP Report to the Commission in Relation** to Article10 of Regulation 141/2000 on orphan medicinal products Doc. Ref. (Final) EMEA/35218/2005. http://www.emea.eu.int/pdfs/human/comp/3521805en.pdf

60. **Guideline on the format and content of application**s for designation as orphan medicinal products. ENTR/6283/00., October 2006
http://www.emea.eu.int/docs/human/comp/628300an.doc

61. **Inventory of Community and Member State' incentives measures to aid the research, marketing, development and availability of orphan medicinal product, Revision 2005**
http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf

62. **EMEA Public Statement for fee reduction** for Designated Medicinal Products, London 18 December, EMEA 4042-01-Rev 7, from 18 December 2006 http://www.emea.europa.eu/pdfs/human/comp/404201en.pdf

63. **Commission Regulation (EC) No 2049/2005,** of 15 December 2005, laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises *(Official Journal L 329, 16/12/2005 p. 4 - 7*

64. **Compassionate use for centralised medicinal products**, EMEA/CHMP/72144/2006 of 20 March, 2006 http://www.emea.europa.eu/pdfs/human/euleg/7214406en.pdf

65. **Guideline on compassionate use** of medicinal products, pursuant to article 83 of Regulation (EC No 726/2004, EMEA EMEA/27170/2007 from 17 of July 2006. http://www.emea.europa.eu/pdfs/human/euleg/2717006enfin.pdf

66. **Commission Regulation (EC) No 507/2006 of 29 March 2006** on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council *(Official Journal L 92, 30/3/2006 p. 6 - 9).* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

67. **Guideline on the scientific application** and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human falling within the scope of regulation (EC) No 726/2004, EMEA/509951/2006 http://www.emea.europa.eu/pdfs/human/regaffair/50995106en.pdf

68. **CHMP-Post-Authorisation Guidance**. EMEA/H/19984/03 rev. 7 corr. London June 2007. http://www.emea.eu.int/htms/human/postguidance/1998403en.pdf

69. G**uidelines on procedures for granting of a MA under exceptional circumstances**, pursuant to article 14 (8) of Regulation (EC) No 726/ 2004, (EMEA/357981/2005), London, 15 December 2005. http://www.emea.eu.int/pdfs/human/euleg/35798105en.pdf

70. **The Treaty of Accession 2003** of the Czech Republic, Estonia, Cyprus, Latvia, Lithuania, Hungary, Malta, Poland, Slovenia and Slovakia Signed in Athens on 16 April, 2003 http://europa.eu.int/comm/enlargement/negotiations/treaty_of_accession_2003/treaty_accession_16.htm

71. **Best Practice Guide** for the Reference Member State in MRP and DP, December 2001 Revision 1 July .2006. http://www.hma.eu/uploads/media/bpg_rms.pdf

72. **Potential serious risk to public health in the context** of Article 29(1) and (2) of Directive 2001/83/EC *(Official Journal C 133, 8/6/2006 p. 5 - 7)* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

73. **Commission Communication from C28/2016 of 16 July 1998**, http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

74. **CMD(h) Best Practice Guide for the public assessment report in the decentralised and mutual recognition procedures** 2006
http://www.hma.eu/uploads/media/BPG_PAR.pdf

75. **Notice to Applicant -Volume 2A. Chapter 2, Procedures for marketing authorisation**, MRP and DP February 2007.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/a/vol2a_chap2_2007-02.pdf

76. **Notice to Applicant -Volume 2A. Procedures for Marketing Authorisation.** Chapter 3.Community Referral, February 2004, Rev.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/

77. **List of referral for human medicinal products**
http://www.emea.europa.eu/index/indexh1.htm

78. **Council Directive 92/73/EEC** of 22 September 1992 widening the scope of Directives 65/65/EEC and 75/319/EEC on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to medicinal products and laying down additional provisions on homeopathic medicinal products *Official Journal* L 297 , 13/10/1992 p 1245-130.

79. **CPMP Public statement on List on Herbal Drugs with serious risk dated 1992**. Doc. Ref. EMEA/HNPC/246736/2005. London, 23 November 2005. http://www.emea.eu.int/pdfs/human/hmpc/24673605en.pdf

80. **Herbal medicinal products in the European Union.** Study carried out on behalf of the European commission AESPG. Pharmaceutical Policy and Law 2.IOS Press (1999) p.55-199.

81. **Report from the ad hog Working** Group on Herbal Medicinal Products 1997/1998. EMEA/HMPWP/25/99. http://www.emea.eu.int/pdfs/human/hmpwp/002599en.pdf

82. **Mandate for the EMEA Working party on Herbal Medicinal Products**. London, 10 February 1999, EMEA/HMPWP/4/99.
http://www.emea.eu.int/pdfs/human/hmpwp/002899en.pdf

83. **Herbal-EMEA Implementation of the New EU Pharmaceutical Legislation,** http://www.emea.europa.eu/htms/general/direct/legislation/legislationherbal.htm

84. **Meeting of the EMEA** working Party on Herbal Medicinal Products 28-29 October 1999, EMEA/HMPWP/32/99 rev.1.
http://www.emea.eu.int/pdfs/human/hmpwp/003299en.pdf

85. **Committee on Herbal Medicinal Products** Guideline on the clinical assessment of the fixed combinations of herbal substances and herbal preparations. London 29 July 2005. Doc. Ref. EMEA/HMPC/166326/2005.
http://www.emea.eu.int/pdfs/human/hmpc/16632605en.pdf

86. R**ecording of core-data for Herbal substances**/Herbal preparations EMEA/HMPWP/41/01, Rev 3.
http://www.emea.eu.int/pdfs/human/hmpwp/004101en.pdf

87. **European Directorate for the Quality of Medicines** (EDQM) http://www.pheur.org

88. Committee for Medicinal Products for Human use, January 2006, Plenary Meeting, EMEA/CHMP/35006/2006,
http://www.emea.europa.eu/pdfs/human/press/pr/3500606en.pdf

89. **Carpener D**. et all. Accelerating approval times for new drugs in the US. *RAJ Pharma*. June 2004, p. 411-417.

90. **Commission Regulation 2049/2005** laying down special financial and administrative provisions for SMEs has been adopted on 15.12.2005 and published on 16.12 in the *EU Official Journal* L 329.15/12/2005, p.4-7.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

91. **Authorisation of medicines**: Commission makes life easier for SMEs IP/05/1618
http://europa.eu/rapid/pressReleasesAction.do?reference=IP/05/1618&format=HTML&aged=0&language=EN&guiLanguage=en

92. **Ericson M. et all.** Compassionate use requirements. RAJ Pharma.Feb 2005, p.83-88.

93. **Arbussa J. M. Some problematical aspects of** the European regulation of medicinal products 2004. Pharmaceutical Policy and Law 6. IOS Press (2005), p. 123-137

94. **Paal T. L. et all** Compassionate use in Hungary. *RAJ Pharma*. Sept 2005, p. 651-652

95. **Guideline on Risk Management Systems for Medicinal Products for Human use ...** EMEA/CHMP/96268/2005,14
Nov.2005 CHMPwww.emea.europa.eu/pdfs/human/euleg/9626805en.pdf

96. **DCP - Decentralised procedure.** Head of Medicines Agencies,
http://www.hma.eu/92.html#c354

97. **Flow Chart of the Decentralised Procedure**, MRFG, 25 July 2005,
http://mri.medagencies.com/mrfg/docs/dcp/dcp_flowchart.pdf

98. **About MRFG, MRFG Activities** http://www.hma.eu/89.html

99. **Co-Ordination Group for Mutual Recognition and Decentralised Procedures** (Human**)** http://www.hma.eu/84.html

100. **98/C 229/03 Commission communication** on the Community marketing authorisation procedures for medicinal products *Official Journal* C 229, 22/7/1998 p. 4 - 17.

101. MRI Mutual recognition product index
http://www.hma.eu/mri.html

102. **Guideline on changing the classification** for the supply of a medicinal product for human use, European Commission, January 2006. ttp://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/switchguide_160106.pdfOTC switch

103. **Cranz H.** Opportunities and challenges for the self-care industry after the revision. Pharmaceutical Policy and Law 6. IOS Press, 2005, p. 95-103.

104. **Nistico G**. Implication of the new directive on traditional herbal medicinal products Pharmaceutical Policy and Law 6. IOS Press, 2005, p. 105-106.

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