# Challenges For The Pharmaceutical Legislative Implementation In Terms Of An Accelerated Market Access After October 2005

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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 |
| CMS | Concerned Member State |
| CMSs | Concerned Member States |
| COMP | Committee for Orphan Medicinal Products |
| CP | Centralised Procedure |
| CVMP | Committee for Medicinal Products for Veterinary Use |
| DP | Decentralised Procedure |
| DAR | Draft Assessment Report |
| EC | European Commission |
| EEC | European Economic Community |
| EU | European Union |
| EMEA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| FAR | Final Assessment Report |
| FUMs | Follow-up Measures |
| HMP | Herbal Medicinal Product |
| HMPC | Herbal Medicinal Products Committee |
| ICD 10 | International Classification of Diseases 10 |
| INN | International Non-proprietary Name |
| MA | Marketing Authorisation |
| MAA | Marketing Authorisation Application |
| MAH | Marketing Authorisation Holder |
| MRFG | Mutual Recognition Facilitation Group |
| MRP | Mutual Recognition Procedure |
| MP | Medicinal Product |
| MS | Member State |
| MP | Medicinal Product |
| NtA | Notice to Applicant |
| NCE | New Chemical Entity |
| NCAs | National Competent Authorities |
| OMP | Orphan Medicinal Product |
| PAR | Public Assessment Report |
| PIL | Patient Information Leaflet |
| PIM | Product Information Management |
| PrAR | Preliminary Assessment Report |
| QRD | Quality Review of Documents Group |
| RMP | Reference Medicinal Product |
| RMS | Reference Member State |
| RSI | Request for Supplementary Information |
| SA | Scientific Advice |
| SMEs | Small and Medium-sized Enterprises |
| SRP | Simplified Registration Procedure |
| SmPC | Summary of Product Characteristic |

| | |
|---|---|
| SOs | Specific obligations |
| SOP | Standard operating procedure |
| WHO | World Health Organisation |

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# 1. Introduction

## 1.1. Legislative health and pharmaceutical framework on the background of the EU development

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. Since the beginning, the Community has grown larger and more countries were gradually involved. However, the 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 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. For the Directive, which is based on article 95, the European Parliament established it in co-operation with the Commission and the Council, the so-called co-decision procedure, in which the member state governments were represented at ministerial level. These Directives are the highest level of legislation. (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 European Union (Maastricht Treaty, 1992) and the Treaty of Amsterdam (1997) have changed the work of the European Union and extended their 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 through 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 among 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 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". The 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 provision 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 in respect of medicinal products, Directive 65/65/EEC was published. The direct cause of the development and implementation in 1965 of the first Directive 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. In order to remove obstacles to the internal market of pharmaceuticals while at the same time ensuring a high level of public health protection, since 1965 the Community has gradually developed a harmonised legislative framework for 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. Over 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 (MP) can only be placed on the market in the Community once they have been granted a marketing authorisation. The marketing authorisation procedures 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 three separate procedures for receiving a marketing authorisation for a medicinal product. The Centralised Procedure (CP) system was initially set up in 1993 with the main idea to improve the assessment and to reach a rapid market access throughout the European

Union (EU). In general, EU pharmaceutical regulations and directives have gone a long way from their initial establishment in 1965 to date (see Table 1).

### Table G1. Development of the EU Pharmaceutical legislation for human medicinal products from 1965 to 2006

| 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 22 , 9 Feb 1965, p. 3 |
| 1975 | Council Directive 75/318<br>Council Directive 75/319<br>Council Directive 75/320 | Admission requirements<br>Action for proprietary MP and Comm.<br>Rules for Pharmaceutical Comm. | OJ L 147, 9 June 1975, p. 1<br>OJ L 147, 9 June 1975, p. 13<br>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,<br>Council Directive 87/21/EEC<br>Council Directive 87/22/EEC | Amended Dir. 65/65/EEC<br>Data exclusivity for innovative MP<br>For placing high-technology MP, derived from biotechnology | OJ L 015, 17 Jan. 1987, p. 36<br>OJ L 021, 23 Jan. 1987, p. 78<br>OJ L 015, 17 Jan. 1987, p. 38 |
| 1989 | Council Directive 89/105/EEC,<br>Council Directive 89/341/EEC<br>Council Directive 89/342/EEC<br>Council Directive 89/343/EEC<br>Council Directive 89/381/EEC | Pricing and Reimbursement of MP<br>Administrative action to proprietary MP<br>Immunological provision for MP<br>Provisions for radiopharmaceuticals<br>Provision for MP - human sources | OJ L 40, 11 Feb 1989, p. 8<br>OJ L 176, 23 June 1989, p. 55<br>OJ L 142, 25 May 1989, p. 14<br>OJ L 142, 25 May 1989, p. 16<br>OJ L 181, 28 June 1989, p. 44 |
| 1991 | 91/356/EEC | GMP principles for MP | OJL 195, 17 July. 1991, p. 30 |
| 1992 | Council Directive 92/25/EEC<br>Council Directive 92/26/EEC<br>Council Directive 92/27/EEC<br>Council Directive 92/28/EEC<br>Council Directive 92/73/EEC | Wholesale distribution of MP<br>Classification of MP<br>Labelling, package leaflet of MP<br>Advertising of MP | OJ L 113, 30 April 1992, p. 1<br>OJ L 113, 30 April 1992, p. 5<br>OJ L 113, 30 April 1992, p. 8<br>OJ L 113, 30 April 1992, p. 13 |
| 1993 | Council Regulation (EEC) 2309<br>Council Directive 93/39/EEC<br>Council Directive 93/41/EEC | Establishment of EMEA and CP<br>Establishment of MRP<br>High-technology MP, derived from biotechnology | OJ L 214, 24 August 1993, p. 1<br>OJ L 147, 24 August 1993, p. 22<br>OJ L 214, 24 August 1993, p. 40 |
| 1995 | Com. Regulation (EC) 540/95,<br>Com. Regulation (EC) 541/95 | Variations CP<br>Variations - MRP | OJ L 55, 11 March 1995, p. 5<br>OJ L 171, 21 July 1995, p. 46 |
| 1999 | Com. Regulation 1999/82/EC<br>Com. Regulation 1999/83/EC | Testing of medicinal products<br>Amended "well established use" | OJ L 243, 15 Sep. 1999, p. 7<br>OJ L 243,15 Sep. 1999, p. 9 |
| 2000 | Directive 2000/38/EC<br>Regulation (EC) 141/2000<br>Com. Regulation (EC) 847/2000 | Administrative action relating to MP<br>Orphan medicinal products<br>Designation criteria of orphan MP | OJ L 139, 10 June 2000, p. 28<br>OJ L 018, 22 Jan. 2000, p. 1<br>OJ L 103, 28 April 2000, p. 5 |
| 2001 | Directive 2001/20/EC<br>Directive 2001/83/EC | Clinical Trials Directive<br>Codification of the EU human pharmaceutical directives | OJ L 121, 01 May 2001, p. 34<br>OJ L 311,28 Nov. 2001, p. 67 |
| 2003 | Commission Directive 2003/63/EC<br>Regulation (EC) 1084/2003<br>Regulation (EC) 1085/2003 | Replaced Annex I of D. 2001/83/EC<br>Variations MRP<br>Variations - CP | OJ L 159, 27 June 2003, p. 46<br>OJ L 159, 27 June 2003, p. 1<br>OJ L 159, 27 June 2003, p. 24 |
| 2004 | Regulation (EC) 726/2004<br>Directive 2004/24/EC<br>Directive 2004/27/EC<br>Directive 2004/98/EC | EMEA, Centralised Procedure<br>Herbal Medicinal Products<br>Data Exclusivity -MRP/DP<br>Blood Products | OJ L 136, 30 April 2004, p. 1<br>OJ L 136, 30 April 2004, p. 34<br>OJ L 136, 30 April 2004, p. 34<br>OJ L 136, 30 April 2004, p. 34 |
| 2005 | Commission Directive 2005/28/EC<br>Commission Regulation2049/2005 | GCP, manufacturing and import-IMP<br>Financial and administrative provisions for SMEs | OJL 91, 9 April 2005, p. 13<br>OJL 329, 15. Dec. 2005, p. 4 |

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 new Regulation 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 Agency for the Evaluation of Medicinal Products (EMEA). **Regulation (EEC) 2309/93,** which entered into force in 1995, introduced the Centralised Procedure and was subsequently revised 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 has to be used by the applicant whenever an application for marketing authorisation for a medicinal product concerns two or more Member States (MSs) with a national marketing authorisation already 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 the Member State (MS) for 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 Authorization. (9, 12, 13)

Regulation 2309/93, Article 71, has 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 procedure applied under Regulation 2309/93/EEC, Chapter III of Directive 75/319/EEC, and Chapter IV of Directive 81/851/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. 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 products 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 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 from 1st of May 2004. (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 were established. (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 substitute the existing Community Code - Directive 2001/83/EC, have come into effect as from October 30, 2005. Directive 2004/27/EC introduced a new Decentralised Procedure and updated the Mutual Recognition Procedure of 1998 and the Directive 2004/24/EC regulating the provisions for homeopathic and herbal products where a Simplified Registration Procedure was introduced with the responsibilities for the herbal medical products of a new EMEA Committee. (13, 19, 20)

The **Work Programme 2005 of the EMEA** was focussed on the preparation for full implementation of the new legislation coming in force in November 2005. Special emphasis is 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 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) are published as part of the monthly CHMP report. (22)

The legislative pharmaceutical documents in force since autumn 2005 are focused on **accelerated assessment procedures**, **conditional authorisation, and compassionate use** procedure for a rapid availability of innovative medicines for patients. In addition, the offered new possibilities for generic products provides 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 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, wherever the dossier is incomplete, have been established. At Member States' level the new decentralised way of authorisation is still in force as of 30 October 2005. (11, 19, 23)

Simplified registration procedure for homeopathic and herbal medicines should provide new advantages for MPs in terms of their rapid market access. All these procedures will have their challenge till accumulating experience and knowledge 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 implementation of the new legislation, also plans 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. (24)

Initiatives outlined in the EMEA's Road Map coupled with the implementation of the new pharmaceutical legislation will 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.

### 1.3. Issues under examination

- To survey the regulatory frame of Data Exclusivity period in terms of accelerated market access in the EU.
- To survey the regulatory frame of marketing authorisation procedures of medicines which lead to accelerated market access in the EU.
- To survey the regulatory frame of the arbitration procedures which lead the medicines faster to the EU.

### 1.4. Methods

- Comparative analysis of 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 in Directive 2004/24/EC, 2004/27/EC.(13, 20)

## RESULTS

# 2. EU regulatory framework of Data Exclusivity protection of medicinal products

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

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

The data exclusivity system for medicinal products exists 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. Many biotechnological medicinal products could not be protected by using patent legislation and data exclusivity, which was introduced to prevent the development of innovative medicinal products from being hindered for a certain period of time. 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 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 receive market exclusivity. Data exclusivity was provided in Article 10 (1) (a) of Directive 2001/83/EC and amended with Directive 27/2004/EC. (13, 19)

The new text in Directive 27/2004/EC, Article 10.2, clarifies what is a **"reference medicinal product"** and a **"generic medicinal product"** and for the first time in the European pharmaceutical legislation provides such definitions. The term "essentially similar" is defined in Directive 2003/63/EC amending the annex of Directive 2001/83/EC to incorporate a common technical document. 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 (13,26,27,28).

**The definition of "line extension"/concept of "global marketing authorisation"** is 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 authorisation 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. No legal issue on the various immediate-release oral pharmaceutical forms existed till Directive 2004/27/EC. The explanations in that direction were based on the Notice to Applicant (NtA) from 2004, after the European Court of Justice Case (29 April 2004 - Novartis, C-106/01), (See Table 2). (13, 26). Modified release products or other dosage forms as line extensions to Article 10 (2) (a), 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)

Another important step is that Article 10.1 in 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 innovative product to be or to have been authorised in one Member State for further marketing authorisation applications in other Member States, where the product is not or has not been licensed. (13)

The documentation requested must be relevant for the assessment of the submitted generic medicinal product. A serious challenge for this process of submitting a generic application is the absence of an official EU Data Base with reference products as this kind of information is only available for products authorised under the Centralised Procedure and consequently published on the website of EMEA ((Article 13 (3) of Council Regulation (EC) 726/2004)). The legal basis for its creation and availability was set out in Article 12 (4) of Council Regulation (EEC) 2309/93. The European Public Assessment Report (EPAR) is a concise document, which highlights the main parts of the CPMP scientific discussion leading to the CPMP opinion. The content of the EPAR is derived from the reports produced during the review of the documentation submitted by the applicant together with the scientific discussion at CPMP meeting. (10, 29)

The generic applicant can use different ways for collecting such information, from the various homepages of the competent authorities in the EU, or the access to the authorised medicinal products is permitted only against payment. (30)

Yet, there is no explicit supervision or sanction in Review 2005 for a situation when the respective Member State would not provide the requested information, e.g. the full composition of the MP in question, on time or when the same MS provides it in the national language. (31)

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) (30) The general requirements for generic products are not sufficient for biosimilar products because the changes in manufacturing process are likely to generate significant differences in terms of quality, safety, and efficacy. The efficacy and safety of the 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 will be determined on a case-by-case basis in consideration of various factors. According to the updated 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 the companies will manage after scientific advice by EMEA and after its 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 practical decision to obtain MA. The process for marketing authorization and preparation of biosimilar medicinal products will be clearer and more precise than in the past, where even in case of a positive opinion of CHMP like Somatotropin – trade mane Omnitrop (London, 26 June 2003, CPMP/3184/03) there is no marketing authorisation on Somatotropin available on the Community Register website. Omnitrop was considered a novel medicinal product and therefore cannot be considered to have well-established use. (35, 36, 37)

### 2.2. New EU harmonized legal framework for the "data exclusivity period"

The EU Pharmaceutical Legislation 2004/27/EC, Article 10.1, and Regulation 726/2004, Article 14. (11), have created a harmonised EU eight-year data exclusivity provision with an additional two-year market exclusivity provision. This effective **10-year market** exclusivity 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 expected/claimed 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 new Member States 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 the results of pre-clinical tests or clinical trials and can demonstrate 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 than eight years in 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 from 10 years to eight years for products approved centrally, as well as for products authorised by national or mutual recognition procedure in the eight MS, i.e. Belgium, Germany, Luxemburg, France, Italy, the Netherlands, Sweden, and the UK. The introduction of an identical data protection period 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 six-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 will be valid for all MP the dossiers of which are submitted before 30 October 2005. This means that the results of the change will only be discernible six years from that day for all new MS as a consequence of joining the EU, the data exclusivity has increased dramatically in some cases from no period at all to 6 years. If the extension to 10 years were to operate immediately, this could lead to serious undesirable consequences for the affordability of the medicinal products to all these markets. The new periods of the 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. (31)

### 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 should be provided to further improve existing medicinal products, in particular to develop new and important therapeutic indications. Such an incentive will be 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 the 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.

The introduced Article 10 (5) also allowed 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 72/2004 start to apply may benefit from a year of protection. (11, 31)

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. (39) The novelty of the indication for 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. (23, 39)

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 a new indication and the current International Classification of Diseases 10 (ICD 10) should be used as bases for diseases' classification. Examples, which are not considered to provide significant clinical benefit, are presented in the same draft guidelines. 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 start to be applied. The 1 year period of protection covers significant pre-clinical and clinical trials conducted for the purpose for a change of application. The competent authorities must assess whether the change is based on significant preclinical and clinical test upon Article 74a of Directive 2001/83/EC as amended (31).

### 2.6. "Bolar' Provision

The review introduced a so called "Bolar" provision in the Community, which relates to patent law and allows the generic industry to carry out the 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. (31, 42, 43).

The new legislation concerning "Bolar" provision provides the opportunity of undertaking commercial development activities clinical trial in the EU, while the reference product is completely protected by patent. (31, 44)

### 2.7. Single data base on the reference medicinal product in the EU

To date, there is no single data base on reference medicinal products in the EU does not exist. The Community register provide information only for the centralised authorised medicinal product. However, for all reference medicinal products authorised at MS level there is no single official data base; in contrast, the FDA has an official site providing information for reference products, the so-called "Orange Book". (45, 46)

**Figure 1. Harmonisation of data exclusivity process in EU-MS acc. Regulation (EC) 726/2004/EC and Directive 2004/27/EC**

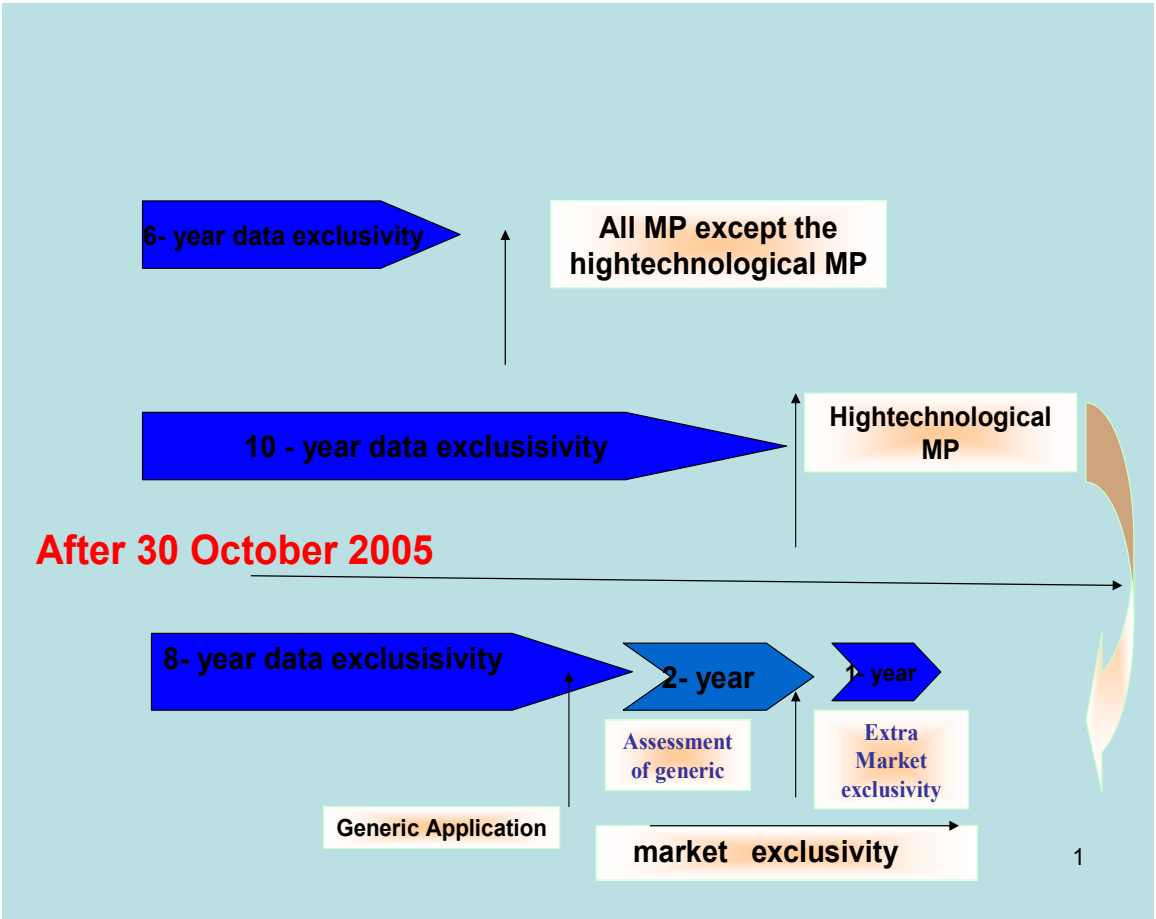


**Table 2. Data Protection period of Reference Product according to Directive 2001/83/EC, Regulation (EC) No 2309/93 and Directive 2004/27/EC, Regulation (EC) No 726/27/)**

| Issue | **Data exclusivity**<br>**Directive 2001/83/EC**<br>**Regulation (EC) 2309/93** | **Data exclusivity**<br>**Directive 2004/27/EC**<br>**Regulation (EC) 726/27/EC** |
|---|---|---|
| Data exclusivity by CP Procedure | 10 years for MP submitted through CP (EEC) 2309/93<br>till 20 November 2005 | **8 years** for MP submitted through CP (EC) 726/2004<br>after 20 November 2005 |
| Market exclusivity | 10 years + period of first MA for similar MP for MP submitted through CP (EEC) 2309/93<br>(till 20 November 2005) | **10 years** for MP submitted through CP (EC) 726/2004<br>after 20 November 2005 |
| 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 |
| 10 years Data exclusivity period | Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Sweden, and the UK.<br>(Single decision procedure of MS | Belgium, Germany, France, Italy, Luxembourg, the Netherlands, Sweden and the UK.<br>**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 10 new Member States<br>(Single decision procedure of MS) | **6 years data exclusivity no more allowed only in Transitional period Directive 2001/83/EC as amended Article 2 in Dead-lines for the transposition** |
| Definition of reference medicinal product | **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 applies 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**<br>Legal definition is in Directive 2004/27/EC Article 10.2b |
| Additional protection for new indication | **No legal issue exist** | Additional protection for new indication Directive 2004/27/EC Article 10.1 |
| Line extension protected by a separate exclusivity period | **Unclear Situation**<br>ECJ 29 April 2004 (Novartis, C-106/01)<br>NTA stated that the data exclusivity is not vested in the dosage form, strength, schedule | **No additional data exclusivity for a Line extension**, Article 6 2001/83/EC, which is part of the same global marketing authorisation dossier as the initial MP |
| Obligation for the reference medicinal product to be on the market where the GP is to be marketed | **Yes**<br>Directive 2001/83/EC<br>Article 10 (iii)<br>Marketing Authorisation prior to the withdrawal of the reference product (Astra Zeneca Case) | **No**<br>Directive 2004/27/EC Article 10.1<br>it is sufficient that the reference product is or has been authorised<br>(RP could be even withdrawn) |

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

## 3.1. Legal issue of Community Authorisation

### 3.1.1. Development of Centralised Procedure

In the European Union, medicinal products can only be placed on the market once they have been granted a marketing authorisation since the implementation of Council Directive 65/65/EEC. With Article 11-13, Directive 75/319, a Committee for evaluation of particular pharmaceutical medicinal products was established – Committee for Proprietary Medicinal Products (CPMP). Nowadays, the Committee became the Committee for Medicinal Products for Human Use (CHMP). That Committee gives an opinion whether a particular medicinal product complies with the requirements set out in Directive 65/65/EEC. The marketing authorisation of proprietary medicinal product under the centralised evaluation 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 (in force from 1995). In addition, it laid down Community procedures for authorization 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 work together in order to provide the scientific evaluation and decision on a marketing authorisation application. 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 the general opinion within all interested parties and the Commission report from year 2001 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 justified a review of the assessment procedures where solutions had been needed in situations not covered by the existing medicinal legislation till 2004. (16, 17)

The objectives set by the Commission Report in 2001 resulted in many new legislative changes in the Centralised Procedure that occurred with Council Regulation 726/2004. Regulation 726/2004 had replaced Regulation (EEC) 2309/93 and the new Directives had introduced amendments to the existing Community Codes on human and veterinary medicines (Directives 2001/83/EC and 2001/82/EC). As a consequence of the revised EU pharmaceutical legislation, the name of the EMEA had changed from the 'European Agency for the Evaluation of Medicinal Products' to the 'European Medicines Agency, nevertheless the acronym 'EMEA' remained unchanged. (11)

The medicinal Community Procedure leads to a single marketing authorisation valid throughout the whole enlarged EU Community, which is granted in the form of a Commission decision and is based on a scientific evaluation by the Committees, created 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.

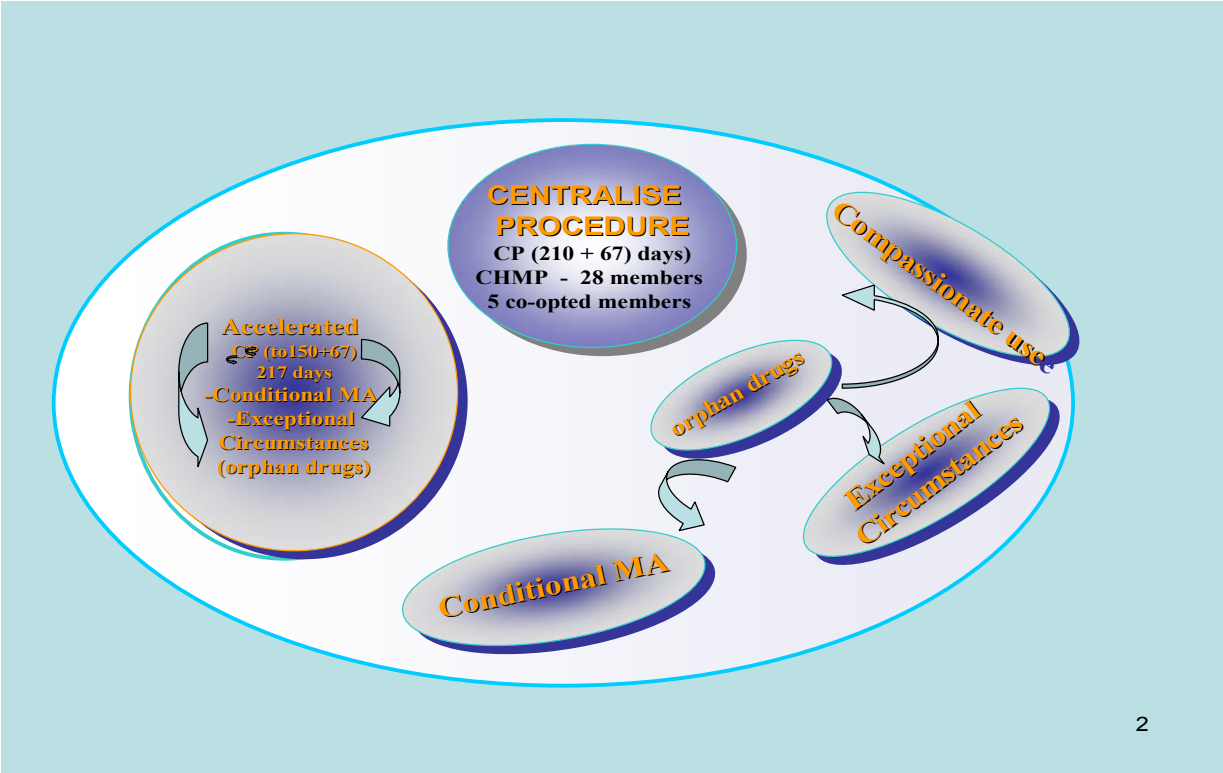
For human medicinal products, the scientific evaluation of applications is undertaken within 210 days by the CHMP. The CHMP has one representative per EU MS (and an alternate). In addition, the new legislation gives the CHMP the possibility of appointing up to

five co-opted members to gain additional expertise in particular scientific areas. The CHMP elected five co-opted members, who joined in September 2004, with specific areas of complementary expertise. In addition, each of the European Economic Area (EEA) - States (Iceland, Liechtenstein and Norway) nominates a member and an alternate. The Committee – through the respective Rapporteur and Co-rapporteur – contracts out assessment work to experts in the Member States. Scientific advisory group is established to provide advice to the Committee in connection with the evaluation or specific types of MP or treatments (48, 49)

During the review process, 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 conclusion 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. (11, 49)

Important new features were introduced in 2005 including an expansion of the scope of the procedure, shortening the process for the Commission decision, and establishment of new specific marketing authorisation procedures, like a Conditional Marketing Authorisation, Compassionate Use, an Accelerated Marketing Authorisation Procedure (fast track procedure), and making available scientific assistance for small and medium-sized enterprises, where the new Regulation from 16 of December was introduced. (Figure. 2)

**Figure 2. Centralised marketing authorisation procedures of MP in the EU Regulation (EC) 726/2004**



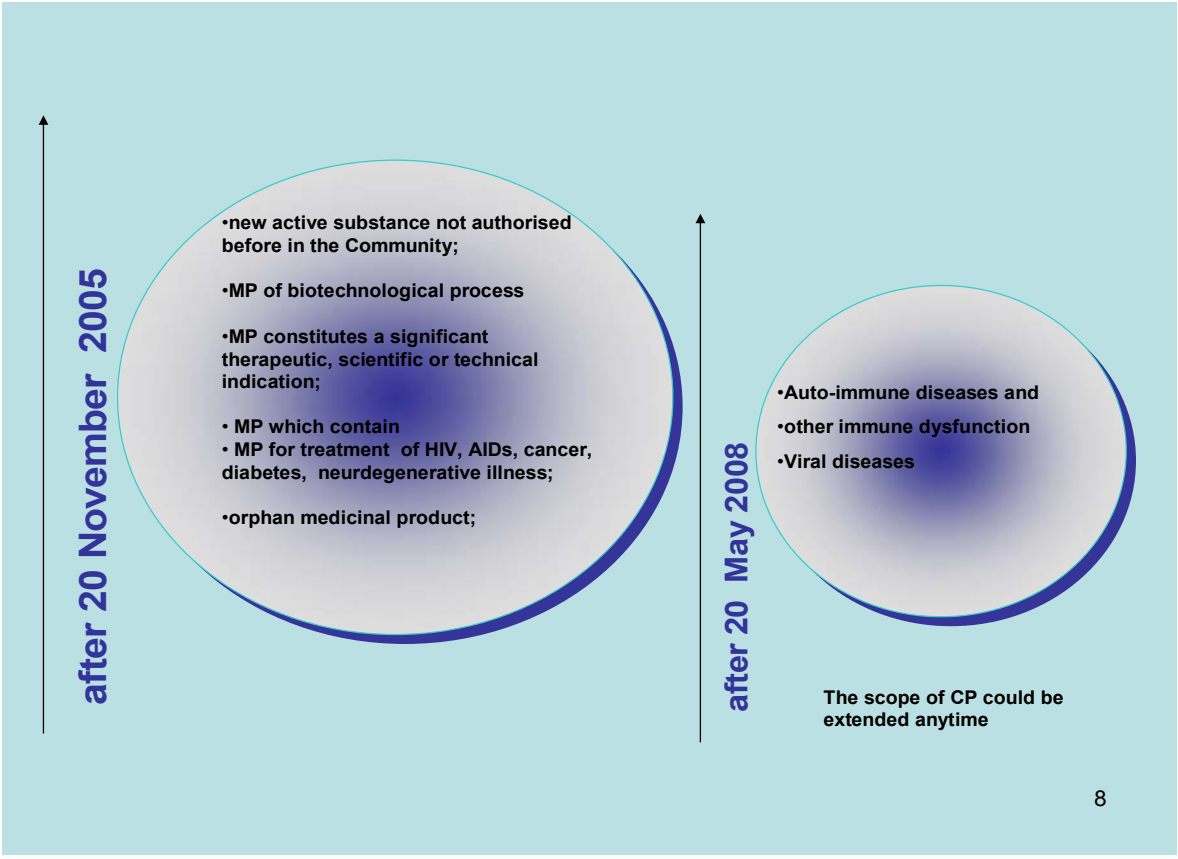

### 3.1.2. Extending the scope of the Centralised Procedure

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). Areas of medicinal human products regulation that have to be authorised at Community level are broadly extended in the scope of the 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, neurdegenerative disorder, and diabetes have been included since 20 November 2005. (11, 50)

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 draft of the EMEA guideline (EMEA/282954/2005) the procedure for confirmation of the eligibility to the Centralised Procedure and the criteria of new active substance not authorised in the Community are presented. (11, 51)

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



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

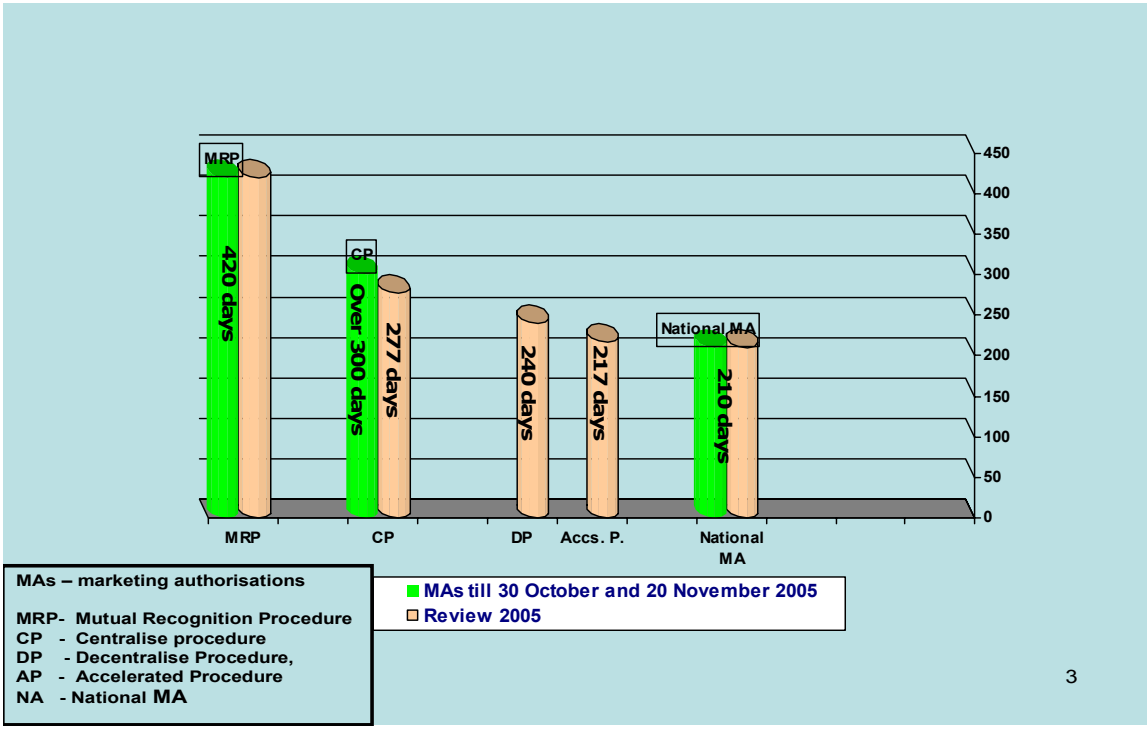
| TOPIC | Central MA Procedure/ Regulation (EEC) 2309/93 (before 20 November 2005) | Central MA Procedure Council Regulation 726/2004 (since 20 November 2005) | Advantages for the Council Regulation (EC) 726/2004 which modify Regulation (EEC) 2309/93 |
|---|---|---|---|
| **Centralised procedure (CP)** | Normal CP | Normal CP<br>Accelerated CP | **New Accelerated CP** |
| **Temporary MA within the CP** | 1. Exceptional Circumstances | 1. MA under Exceptional Circumstances<br>**2. Conditional Authorisation**<br>**3. Compassionate use** | Two new temporary procedures within the Centralised Procedure |
| **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<br>**Part A**-biotechnological MP<br>- recombinant DNA technology<br>- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes-transformed mammalian cells<br>**- Part B - not obligatory for the CP** | - New active substance (NAS)<br>- innovative MP<br>- Immunological. MP for the treatment of animal diseases that are subject of prophylactic measures<br>- MPs in Annex - Reg. (EC) No 726/2004 | Generic products could use the option of CP or DP<br><br>**- biosimilar only via CP**<br>**- orphan MP only via CP** |
| **Type of Applications** | **full dossier acc. 2003/63/EC stand alone application**<br>- bibliographic application.<br>- mixed application<br><br>**abridged application.**<br>- informed Consent App.<br>**- essential similar to RP via CP** | **full dossier 2003/63/EC stand alone application**<br>bibliographic application<br>- mixed application<br><br>**abridged application**<br>- informed consent application<br>**- generic application bioequivalent to RP** | - provision for MA of generic product where the reference product has undergone CP<br>- provision for biosimilar<br><br>- after 8 years of the MA of RP generic application possible |
| **Assessment** | CHMP, CVMP, COMP<br>18 Working Parties | CHMP, CVMP, COMP,H<br>**CMD (h) + 17 Working Parties** | Two new Committees<br>Herbal and CMD (h) |
| **CHMP Opinion SmPC, PIL** | Art.<br>after 210 days | Art 6 (3) After 210 days<br>**Art 14 After 150 days** | **Accelerated assessment in 150 days**<br>**60 days shorter the normal CP** |
| **CHMP send Positive Opinion SmPC, PIL** | **+30 days**<br>**(total 240 days)** | **+15 days**<br>**(CP-225 days)**<br>**Accs. Assessment - 165 days)** | **CP- 15 days shorter time Accs Assessment** |
| **Commission draft Decision** | **+ 30 days**<br>**(total 270)** | **+15 days Art. (10)**<br>**(CP- total 240 days)**<br>**(Accelerated. Assessment CP-180 days)** | **15 days shorter** |
| **Member state Draft Decision** | **+28 days**<br>**(total 298 days)** | **+22 days –**<br>**(CP - total 262 days)**<br>**(Accelerated Assessment-202 days)** | **6 days shorter** |
| **Commission Decision** | **No period fixed**<br>**(over 300 days)** | **+15 days –**<br>**(CP- total 277 days)**<br>**(Accelerated assessment - 217 days)** | **New CP 36 (12%) days shorter than the previous CP**<br>**Accelerated assessment 60 (22%) days shorter than the normal CP** |

In the period 1995-2004 the CP proved its effectiveness in assessing medical 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 medical substances in the mentioned indications to go through the CP.

### 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 Commission decision period was significantly reduced. Till the draft Community Decision the process is decreased by 36 days (see Table 3, Fig 2) 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 clockstop)**




In 2001 EMEA had introduced instruction CMPM/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"). Now the procedure for accelerated assessment is legislatively available. (11, 52)

The legislative pharmaceutical documents in force since autumn 2005 are focused on **Centralised accelerated assessment procedures** (217 days), which is by 60 days (28%) shorter than the normal current CP (277 days). Where the MP is 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 is introduced under the Regulation for the applicant to formally request an accelerated evaluation. For such assessment with which the procedure is 60 (28%) days shorter than the general case in the Centralised Procedure, 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 (EMEA/7358/2005) is still under preparation, which intends to present all details and new steps for the accelerated approval at the Community level. (23)

Requests for an accelerated assessment should be submitted two months in advance with the provision in the EMEA guidance on practical considerations relating to the new legislation for the Centralised Procedure (EMEA/23280/2005). In the previous legislation (before 20 November 2005) such shorter scientific assessment procedure was not legislatively allowed. (53) 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 +36 day) days faster than the normal CP in the previous legislation is set up legislatively requiring enactment of new timetables to comply with the new regulation.

### 3.1.4. Management and exchange of medicinal product information

There are now 21 languages involved in the Centralised Procedure and this is due to increase to 24 in 2007 when Romania and Bulgaria are expected to join the EU and Maltese will become an official language. 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. Product Information Management (PIM) system 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. 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. (54)

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 these standards are 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 will be further developed to support products in the Mutual Recognition/Decentralised and National Procedures. The Coordination Group for Mutual Recognition and Decentralised Procedure - MRP/CMD (h), according to Article 27, Directive 2001/83/EC, as amended, is now proposing the adoption of the QRD templates in MRP/DCP and is also proposing the adoption of PIM. (55)

The implementation of Article 10 (1) 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 will greatly ease these challenges through management of the underlying information and re-use of repeated information rather than a focus on the very documents. Once PIM is established for the Centralised Procedure, it is anticipated that the use of the system will be expanded to include the Decentralised, Mutual Recognition, and National Procedures

### 3.1.5. New regulatory issue of orphan medicinal products

Over 8000 different rare disorders have been identified worldwide. In the EU, with great variety of population groups, 25-30 million patients have rare diseases, while in the US 10 to 20 million patients are affected. (56) European Union orphan medicines legislation was introduced in 2000 and gives 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 date are for rare diseases in oncology and more then 65% of the designations are for diseases in children. (57)

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. (58)

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 is published as a contribution to support the European Commission in finalising its general report before 22 January 2006.

With the Annex of new Regulation (EC) 726/2004, the Centralised Procedure is mandatory for all marketing authorisation applications relating to designated orphan medicinal products. Between April 2000 and April 2005, 458 applications for orphan designation were submitted to EMEA. By April 2005, more than 260 products were designated relating to over 200 different rare conditions. (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 the 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 (58):

- 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. (58)

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 authorized and which complies with the requirements for orphan drugs. The marketing authorization holder would be required to apply for separate marketing authorization for the orphan indication. Orphan and non-orphan indications may not be covered by the same marketing authorization. (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 of OMP is granted under CP a 10 ten year data exclusivity period is in applied. This period may be reduced to six years, if at the end of the fifth year if 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 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 than this MP could be authorised like an orphan drug. (58)

The word “condition” is used (rather than disease) to ensure that the regulation applies also to treatments for condition, which are not classical diseases, in particular genetic disorders. The term “condition” is defined in the Guideline (ENTR/6283/00) 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 Regulation (EC) 726/2004, Annex (4) only the CP will be an option for orphan medicinal products. It will be no longer 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 shall be conducted in a transparent way and all parties involved informed accordingly. Marketing authorisation application for designated orphan medicinal products ongoing evaluations in National or Mutual Recognition Procedures must be submitted to the CP after 20th November 2005, unless the Applicant wished to remove the orphan medicinal product designation from the Community register. Orphan designated medicinal products, already approved via a National Procedure (NP) 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. Marketing Authorisation Application must be submitted *via* the Centralised Procedure unless Applicants wished to remove the OMP designation from the Community register. After submission of the dossier to the EMEA, the CHMP evaluation process will proceed according to the current CP. (23, 53, 61)

## 3.2. Temporary Marketing Authorisations of medicinal products

### 3.2.1. Assessment for Compassionate Use of MP

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". 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. The medicinal products concerned must either be subject of an application for a marketing authorisation pursuant to Regulation (EC) 726/2004 or must be undergoing clinical trials (see Figure 5). (11, 31)

**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". (31).

The new legislation for "compassionate use" does not provide legislative recommendations defining the authorisation condition, which must be respected by the Member States. This measure does not replace national legislation but harmonises the criteria according to which medicinal products can be made available to certain patients before the MA is granted. CHMP is presently drafting a guideline (EMEA/CHMP/5579/04) describing recommendations concerning the distribution and choice of patient for those medicinal products falling under the CP. (23)

MS should also put these recommendations should also into place (Article 83 (5) of the same EC Regulation). 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 MP

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 draft Guideline (EMEA/19237/2005) on the application of Article 4 (b), (c), and (d) of the draft Commission Regulation related to Article 14 (7) in accordance with the procedure laid down in Article 87 (2) will be covering Conditional Marketing Authorisation, which includes MP for human use as defined in Articles 3(1) and 3(2) of the same Regulation (see Figure 5). (23, 62)

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 on-going clinical trials or conduct new studies to verify a presumed "positive benefit-risk balance". Article 2 in the draft Commission Regulation on the conditional marketing authorisation for MP falling in the scope of Regulation (EC) No 726/2004 of the European Parliament and the Council of 31 March 2004 providing the scope of the medicinal products which may benefit from a CMA: (62)

- 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.

According to the draft 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 the CHMP may, during the assessment procedure of Article 7 of Regulation (EC) 726/2004, propose a Conditional Marketing Authorisation. 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 Conditional Marketing Authorisation shall be made publicly available.

The requirements according Article 4 to the draft Commission Regulation on the Conditional Marketing Authorisation for the conditional authorisation are:

- the public health interest of the medicinal product;
- positive benefit-risk balance of the medicinal product, based on scientific evidence and pending completion of further studies;
- the quality and, unless duly justified, the non-clinical safety data of the product complies with the requirements laid down in Annex I of Directive 2001/83/EC;
- finalise the on-going studies or conduct new studies for verifying the positive benefit-risk balance and any specific obligation and the time frame for their completion are to be clearly specified in the conditional marketing and shall be made publicly available. (62)

All specific obligations (SOs) 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 Conditional Marketing Authorisation will become a "normal" marketing authorisation. (11) 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. (63)

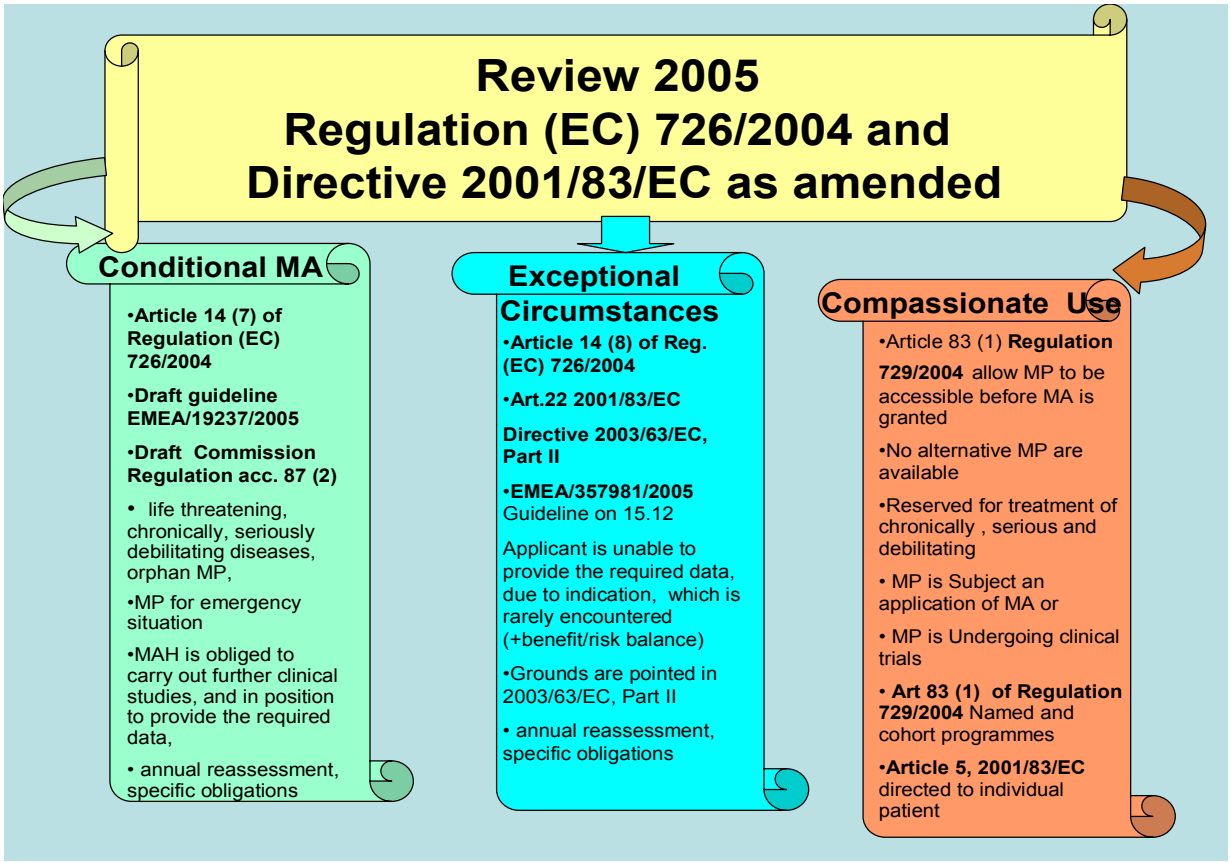
### 3.2.3. Assessment for Authorisation under Exceptional Circumstances of MP

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 generate 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).

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. (64)

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 re-assessment. In addition, any authorisation may be subject to follow-up measures (FUMs) relating to post-approval commitments. .

**Figure 5. Temporary Marketing authorisation of medicinal products**



## 3.3. Legal basis for EU decentralised marketing authorisation of MP

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. A national marketing authorisation procedure according to Article 17, Directive 2001/83/EC, should not take longer than 210 days. Since 1998, 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 concerns two or more Member States. With the Review 2005, the DP has been introduced as an additional procedure. MPs not authorised or with pending authorisation could be placed on the market for justified health reason if possessing authorisation in another MS and national legislative provision should be developed. (31)

### 3.3.1. Scope of the decentralised system

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 October 2008, new chemical entities in the therapeutic indication for the treatment of autoimmune diseases, other immune dysfunctions, and viral diseases could be in the scope of the DR/MRP. Nevertheless, 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.

According to Annex (4) of Regulation (EC) 726/2004, medicinal products with orphan designation fall under the mandatory scope of the CP and may not follow the MRP after 20 of November 2005 Orphan medicinal products cannot be approved under the decentralised system because a significant therapeutic benefit will be provided according to 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, can not be subject of the DP due to the definition provided in the Annex of Regulation (EC) 726/2004 (11).

For the MRP/DP a Co-ordination group, Co-ordination Group for Mutual Recognition and Decentralised Procedures - CMD (h), composed by representatives from each MS, is set up for "examination of any question relating to the MA of MP" in two or more Member States in accordance with the procedures laid down, in the amending Directive 2004/27/EC to the Directive 2001/83/EC as amended. (13,31) According to the amending Directive the CMD (h) is obliged to lay down a list of MPs for which a harmonised SPC should be drawn up. This list shall take into account proposal from Member state and the list of the Commission shall be forwarded to the Commission once a year. (65)

### 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. RMS has 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 Concerned Member State (CMS). Reference Member State is the MS, which has issued the marketing authorisation on which the MRP is based. (66)

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 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 Concerned Member States (CMSs) and to the MAH together with the approved summary of products characteristic (SmPC), labelling and package leaflet (PIL) (See Table 4). (See NTA, Chapter 2, October 2005). (39,67)

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. (67)

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 time 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). (31,66)

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, which is already covered by an existing marketing authorisation in another Member State will have to be considered in the context of the 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. (68)

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) was set up for better covering the market with certain MP. For practical purpose, 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). (68)

### 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 cope of the CP, i.e. like the MP under MRP. The Decentralised Procedure, 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 MP has not yet received a marketing authorisation in the EU. (13, 31)

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 (31) normally initiates the procedure. Once the DP is triggered by the applicant, the DP timelines have to be followed according to the Guidelines on submission dates for the applicants on the Decentralised Procedure and all marketing and post-marketing steps should be followed like the in MRP, by the RMS. The Decentralised Procedure is divided in four steps: pre-procedural step with the validations phase, Assessment step I and Assessment step II including discussion at the CMD (h), if needed, and National step. (70)

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. By day 100, CMSs should communicate their comments to the RMS and applicant and if any issues for "potential serious risk to public health arise" 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. For that period of time RMS stops the clock and restarts the clock on day 106 after receipt of the response. At day 120, the RMS may close the procedure, which continues at national level.

**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. That period includes discussion at the Co-ordination Group for Mutual Recognition and Decentralised Procedures for human medicines CMD (h) set out in Article 27 of Directive 2001/83/EC, 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) (See Table 4). (70, 71, 72)

### 3.3.4. National Step of the decentralised system of marketing authorisation

Normally, both procedures, MRP and DP, follow Assessment steps and the National step. After the different Assessment steps in both MRP/DP presented in "Best Practice Guide for Mutual Recognition Procedure" and in "Member States' Standard operating procedure of the Decentralise procedure", the National Competent Authorities (NCAs) shall adopt a national decisions, 30 days after RMS closes the procedure, the applicant submits high quality national translations of the SPC, PL and labelling later than 5 days after the procedure is closed. The product information is a faithful translation of the final harmonised position. The

'blue box' concept for adequate national information on the label and package leaflet will be permissible and should be taken into account, when finalising national translations. (31, 67, 70).

### Table 4. Comparison between MRP (Directive 2001/83/EC) and MRP/DP (Directive 2004/27/EC and Directive 2001/83/EC as amended)

| Issue | Mutual Recognition Procedure (MRP) 2001/83/EC | Mutual Recognition Procedure (MRP) Decentralised Procedure (MRP/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 MA (210 days)** | **National MA for MRP**<br>**National MA not needed for DP** | For DP no requirements for national approval |
| **Scope of the MRP/DP Procedure** | **MP under MRP**<br>(MP essentially similar to RP under MRP)<br>- new substance, except in Annex Part A, Reg. 2309/93 except<br>- MP of Annex Part B Reg. (EEC) 2309/93, Orphan MP | **MP allowed under DP/MRP**<br>- generic homeopathic<br>- herbal MP<br>- immunologicals MP<br>- blood medicinal products<br>- Possible till May 2008 autoimmune diseases, immune dysfunction, viral diseases | With the Review 2005, the scope of the CP has been extended.<br><br>In consequence, the scope of the MRP/DP has been narrowed. |
| **Application of MP** | RMS from the NA and to CMS's SmPC+PIL | To RMS and to CMS's SmPC+PIL | Different trade Names allowed |
| Type of applications To be applied | **Stand-alone application**<br>Bibliographic applications<br>Mixed application<br>**Abridged application**<br>Inform consent application<br>**Essential similar to RP under CP/MRP** | **Stand-alone application**<br>Bibliographic application<br>Mixed application<br>**Abridged application**<br>Inform consent application<br>**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<br>- application two years before data exclusivity expiration |
| Fee | Fee payment to RMS + the CMS's | Fee payment to RMS + the CMS's | No change in the legal issue |
| Number of Dossiers | To RMS and to CMSc according NtA 2A | To RMS and to CMSs according NtA 2A | No change in the legal issue |
| National Ass. process | **National MA 210 days** | **National Procedure should be finished before MRP**<br>**DP - Start of procedure** | National Procedure is not needed before starting of DP |
| RMS sends an Assessment Report SmPC, PIL to CMSs | **MRP- within +90 days (300 days) Art. 28** | **MRP- within +90 days**<br>**DP - RMS within 120 days Art.28(3)** | Harmonisation process of SmPC, PIL parallel with the Assessment Report |
| CMSs approved Ass. Report and Final Assessment Report (FAR) | + within 90 days **(390 days)** | **MRP+ within 90 days (390 days)**<br>**DP- within 90 days (210 days)** | The duration of the DP is 180 days shorter than the MRP |

## 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. Marketing authorisations granted by the competent authorities of the MS, by the Commission, involving a scientific opinion by the CHMP leading to the adoption of a Commission decision addressed to the Member States, can be triggered. 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, the CMSs in case of a positive outcome will issue national marketing authorisations. Other Member States not directly concerned at the time of the decision are also bound as soon as they receive an 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 of 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 Co-ordination Group/CMD (h). The consideration of issues by the Co-ordination Group 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 (73).

Where the Member States, concerned by the procedure, fail to reach an agreement within that CMD (h) Group, 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 Co-ordination Group and, in absence of an agreement therein, referral to CHMP. The expression "potential serious risk to public health" is defined in a draft which was issued by the Commission in 2005 (74).

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

Arbitration procedure according to **Article 30** is based on several applications, which are submitted as per Articles 8, 10, and 11 of the 2001/83/EC as amended. National authorisations in more than one Member State were possible until 1$^{st}$ 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 will facilitate the above process and will determine the criteria for the selected products (Mutual Recognition Facilitating Group – MRFG meeting in April 2005). Historically, a former Working Group (MRFG) established in 2001 provided information on the aims and timelines for prospective

SmPC harmonisation (CHMP meeting 2002) and the first referrals concerning harmonisation were initiated in November 2002. (75, 76) (See Table 1).

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 new CMD (h) – Co-ordination group. If issues cannot be resolved within 60 days by the new CMD (h) – Co-ordination group, 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 pharma-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. (31)

Compared to the previous arbitration process, according to Articles 32, 33, and 34 of Directive 2001/83/EC, the 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 new CMD (h) Group within 60 days, the procedure will be followed by a national authorisation process, which will not be longer than 30 days.

Such arbitration period for the MP will be 90 days compared to the referral (Directive 2004/27/EC) 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, Directive 2001/83/EC, was 180 days + 30 days national phase and today such process even with the CMD (h) step counts 172 days. (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 of the Assessment Report, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. (31)

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

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

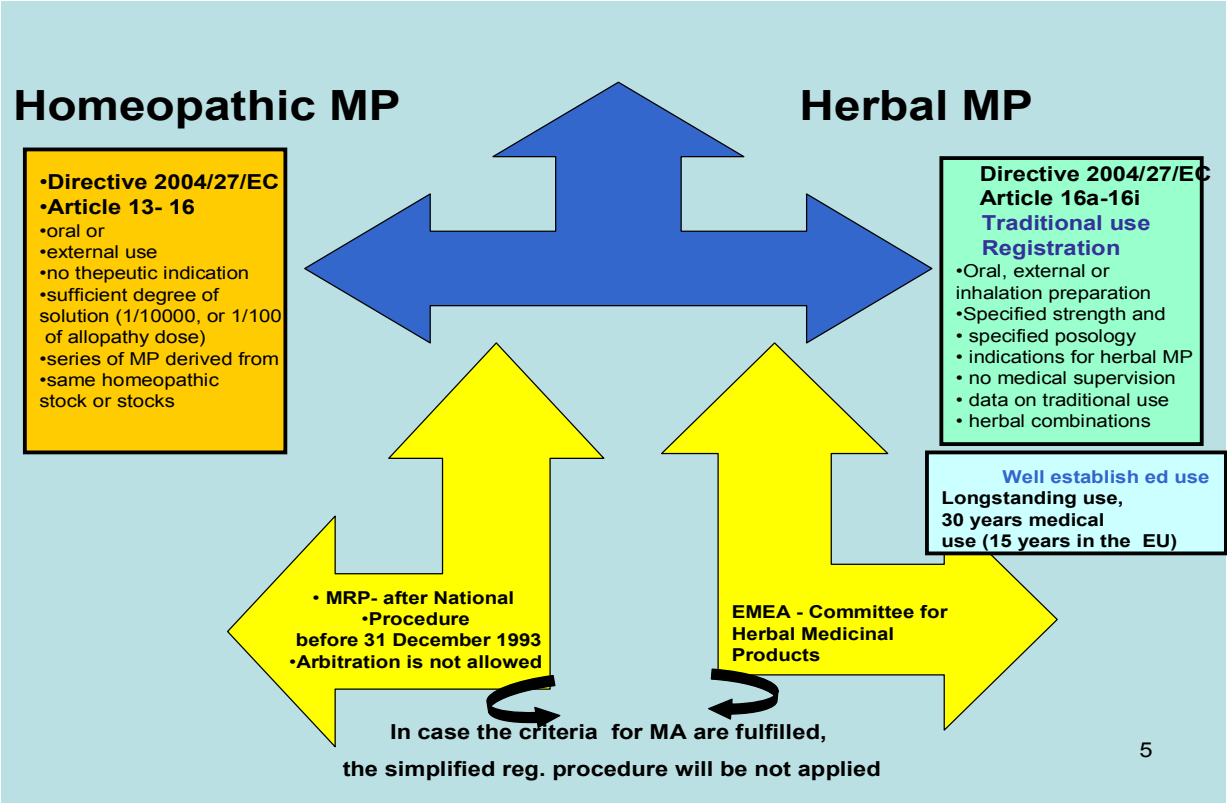
## Table 6. Arbitration Procedure in Directive 2001/83/EC Compared to Arbitration Procedure in Directive 2001/27/EC

| Step of the Referral Procedure | Directive 2001/83/EC (before 30th Oct) MRP, CP | Directive 2001/27/EC (after 30th of Oct) MRP/DP, CP |
|---|---|---|
| 1.MRP structure at the EMEA | MRP Working Party provided information on the aims and timelines for prospective SmPC | Agreement in the Co-ordination Group<br>In 60 days agreement between the CMD (h) member ( Art 29. 3)<br>**CMS adopt decision (30 days national MA)** |
| 2. CMS does not agree. Start of Arbitration procedure | Start of the procedure **0 via the agency CHMP** | (CMD 60 days) in case of disagreement arbitration procedure via the Agency (CHMP)<br>Those CMSs who agree with decision may authorise the product ahead the arbitration. |
| 3. CHMP Opinion (Art. 32) | 1. CHMP opinion within **90 days**<br><br>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<br>within 60 (120) days ( 30 days shorter)<br>(Art. 31, 32 - up to 90 days)<br><br>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. EME -Referral opinion, **Ass. Report, SmPC, PIL** send to the Commission | In + **30 (120)** days | In + **15 (135) days**<br>15 (45) days shorter) |
| 5. Written observation of the MSs to the Commission Draft Decision | In **30 (150) days**<br>should be provided | In + **22 (157) days**<br>+ 8 (53) shorter |
| 6. Final Commission Decision | In **30 (180) days (Art. 34)**<br>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).<br>Decision based on 34 (2) 121 (2) , Art 5 of 1999/468/EC.<br>Negative CHMP opinion or MSs, company appeal, procedure like in point 3.2 of Table5 | **In +15 (172) days** (Art 34)<br>+15 (68) days shorter<br>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.<br>Negative CHMP opinion or MSs, company appeal, procedure like in point 3.2 of Table 5 |

## 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 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. (19, 20) In Figure 6, the criteria of the Simplified Registration Procedure (SRP) for the both classes of MPs are presented.

**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 a marketing authorisation for these products. The different marketing authorisation procedures were on country level and till 1992 there was not EU requirements. The provisions for homeopathic MPs in Directive 92/73/EEC are incorporated in Directive 2001/83/EC and later in 2004/24/EC. (19, 20)

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 that were administered orally or externally and no specific indication appeared on the labelling and the PIL had to be labelled with the specific information presented in Article 7. (77)

The purpose for these is that the normal procedures have been not suitable for homeopathic medicinal products, because the action of the homeopathic medicinal products is not based on the pharmacological action of the substances, but rather on specific homeopathic principles and the clinical test is not compatible with the principle of the homeopathic medicine. Currently, the homeopathic medicinal products are authorised on a purely national basis. (74)

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 such 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 (31)

The requirements of the registration procedure differ in many ways from the 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). The Arbitration procedure of Article 29 (4) to (6) of the same Directive and it 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 all those medicinal products are the same as for the other MPs. (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 Committee for Proprietary Medicinal Products 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 Committee considered that this list was a useful source of information on plants with intrinsic safety risks and therefore it had decided to be published. (78)

Member States had adopted divergent national requirements for herbal medicinal products (HMP), which were presented in a report prepared for the Commission by AESGP in 1999, showing different experience in the different MSs and it was an attempt for comparison of the legal requirements of 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 law. The conclusion of this report stated that two categories exist in many MS; 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. (79).

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 document on the test and trials on safety and efficacy 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. (31,39)

### 3.5.3. Committee on Herbal Medicinal Products (HMPC)

Directive 2004/24/EC, Article 16h had established a Committee on Herbal Medicinal Products (HMPC), which took over the tasks of the CHMP with respect to herbal medicinal products and started work on 23 September 2004. (19)

Formerly, the CHMP was aided in its work on herbal medicinal products by its Herbal Medicinal Products Working Party – HMPWP. Before the HMPWP an ad hoc Working Group on Herbal Medicinal Products was established in 1999. The main task of the report of the 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. The Working group was established on the request of the European Parliament and the European Commission (80, 81).

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. (39)

The Committee will have the discretion, in individual cases, to draw up an opinion on the adequacy, of the evidence, 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. (39, 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). (82, 83)

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. (19)

### 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. (19)

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.

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 submitted, 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. For non-clinical and clinical data guidance is available on the application of non-clinical tests to herbal medicinal products with long-term marketing experience. (30)

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 is the monographs produced by the World Health Organisation (WHO) and ESCOP (European Scientific Cooperative on Phototherapy). 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). (84)

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 (EDQM) (85).

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-Apr-2011. (19)

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## 4. Discussion on challenges in 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 will 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, 86)

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 industries innovative and generic – were in general highly complimentary about the expertise and efficiency of RMS in the period 1998-2004. One of the aspects that come 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 medicinal products 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 serous weak point was that once objections relative to potential serious risk public health have been raised, it often proves 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. There is 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, 86)

Both the Centralised and Decentralised Procedures are 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 that are the transparency and the SmPC and PIL harmonisation process within the new MRP/DP and arbitration procedures.

The overall status of applications has shown a total of 3108 MR Procedures and 23 Arbitrations finalised since 1$^{st}$ of January 1998. Also, all new applications approved under the Centralised Procedure total to 288 MAs granted by the Commission in the period from 1995 till January 2005. During the same period of time, in six 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)

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 eight years for MRP and 10 years for CP, respectively. However, expanding the scope of the

Centralised Procedure to all new drug substances, in pre-defined indications, will increase the future number of centralised applications significantly.

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 the immunological, herbal, homeopathic medicinal products, etc (See Table 4). The future will show how the changes in the new 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 Review 2005, flexibility for the generic applicant, whose reference product has 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 new Review, for the products not obligatory for the CP it will be a company 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 28% 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 "normal" CP (277 days) pursuant to Regulation (EC) 726/2004 as compared to the "normal" CP (300 days and over) in Regulation (EEC) 2309/93) offers also great potential for a faster placing on the market of MPs, which are of major interest from the point of view of public health. Now, pursuant to Article 10 (3) 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 application 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 joined 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, priority 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 (87). The new EU provision for accelerated assessment could provide similar result in the future, shortening the median approval time of MP as the experience with the FDA in the USA. From the other site, is important to emphasise that it is crucial not to facilitate the access of inadequately assessed drugs to the market.

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 individual level and it is related to the interest of the patient and 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 25 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/7358/2005, which is still under elaboration, needs to provide answers to these questions. (23)

The centralised approval system (normally, 277 days) without clockstop 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 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.

The choice of the procedure is of crucial importance for selling and marketing of the medicinal product after MA. 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. (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 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 Annex I to Directive 2001/83/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.

According to 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 re-assessment and certain specific obligations ((Article 14(8) of Regulation 726/2004)). (11)

According to the new pharmaceutical legislation, MP 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 draft Commission Regulation on the Conditional Marketing Authorisations. (62)

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 re-submitted 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, MRFG). (53)

It will be very difficult for small and medium-sized enterprises (SMEs) and companies with a small selected number of EU MS to follow the Centralised Procedure and to pay the EMEA orphan application fee, regardless of all reductions and preferences introduced. According to the new 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. (88, 89, 90 )

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/CHMP/5579/04) with recommendations to be put into practice and to be applied by every Member State. The different MSs should have implemented legislative rules regarding "compassionate use" for products, which could have only a national patient application. (23)

Within the EU, the regulatory supervision of compassionate use is within the responsibility of the national regulatory health 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. (91)

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 clinical 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. (92)

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).

This disharmonisation between the MSs in both options relating to "compassionate use" and "named and cohort programmes" should be 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 database set up according to Article 57 (n) of Council Regulation (EC) 726/2004 will include information on clinical trials (EudraCT) 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 MP 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**. A new 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 .(64)

Clarification is still needed concerning different aspects of MA under exceptional circumstances and conditional MA. The new 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)

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. (64) A Conditional Marketing Authorisation could be granted in the absence of comprehensive clinical data when it is likely that the applicant will be in position to provide such data in a short timeframe, according to Article 4 of the draft Commission Regulation for Conditional marketing authorisation. Further EMEA guidance (EMEA/19237/2005) will provide answers to many questions. (23, 62)

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. (64)

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. (64)

In the newly 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. (66)

In a second step, the so-called "second wave", a further MRP/DP could be initiated with additional MS. 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, sofar 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. The new updated MRP, where claims "potential serious risk to public health" are raised, will also profit 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 proposed guideline, which has been under discussion for nearly a year, is intended to address the problem that arises when one MS refuses to recognize a MA granted by another MS. (74)

The informal Mutual Recognition Facilitating Group (MRFG) has 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 series of procedural documents have also been agreed upon and the Group has played a major role in the ongoing work of 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. (94)

The New 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.

Pursuant to the Pharma-Review 2005 the MRFG is converted to official Co-ordination Group for Mutual Recognition and Decentralised Procedures CMD (h) Group. (31) Although the MRFG's functions were primary regulatory and procedural now the CMD (h) group will also be requested to give scientific opinion. That Group will play leading role in accelerated solving the problem rose in the decentralised system including also discussion at CMD (h) in Assessment step II in DP if needed. (70)

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

Before, the background of selling and marketing also in time the **option "Co-Marketing"** ((second application with the same International Nonproprietary Name (INN) but different trade name and the same or different MAH)) was an option for the decentralised system. In cases via CP where companies wish to market the same MP under more than one trade/invented name, then additional applications for separate authorisation should have to be submitted. Pursuant to Article 82 (1), Regulation (EC) 726/2004, the European Commission should have 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 could be certified by the competent authorities for Co-Marketing in the context of the CP and MRP/DP. (11, 69, 95)

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 market availability of MP for public health reasons.

**The Review 2005 introduced many advantages for the generic medicinal product**, which allow generics to reach the Community market faster. (26,43)

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. (97)

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 article 10 (1) of Directive 2004/27/EC. Although the applicant is not required to provide results of pharmacological and toxicological tests or results of clinical trials, the documentation and data required, as they 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 will refer to the data that have been established in the reference product's application for authorisation. (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 has been withdrawn from a MS, the generic medicinal product could not be placed there either. It can be expected that following to the changes introduced by the Review 2005, many generics will appear in different MS where the reference innovative medicines had never been

marketed. Apparently, that situation is depending on the pharmaceutical market of the MS, especially where the MAH was not motivated to authorise an innovative MP in that country.

**The changes focused 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 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. Because of the lack of such official EU database, like in US, only the chronology in the MA of the innovative medicinal product could find out the searched information. The Co-marketing authorisations could provide additional complication in receiving the objective 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. That 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. (45, 46)

Directive 2001/83/EC does not provide any measures for supervision or sanction in case the competent authority, which has authorised the reference medicinal product, does not submit 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 acceptable for the authority awaiting this information.

With the changes in Article 10 (2) (b) 2004/27/EC giving a clear definition for a "generic products", where "the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form" and it is a clear intention to prevent generic products being blocked by innovative industry making changes to the active substance and gaining an extended protection period (13). The update of the legislation from 2005 in this point is intended to shorten the assessment period of generic products and avoid the innovative industry to involve any law steps in order to prolong their market exclusivity 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) disharmonisation between the "original" and the "reference products" from country to country are probably possible. 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 a biosimilar product will be in fact classified by EMEA as a new application if the RMP has not undergone the Centralised Procedure? The greatest hurdle is that the originator's data often remain inaccessible for cross-reference by a second applicant because most recombinants submitted via the earlier concentration procedure or by National Procedures. (37) A guideline will be needed for such cases where the MS should provide the information of the RMP for the biosimilar medicinal product.

At present, the beginning and 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. 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 MP will be granted a further one year period of protection of the data in the future, if a change of the classification of the medicine, i.e. a switch of the status from "use up requiring" to "pharmacy requiring", 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 delivery status, which refers to the first application. With the Centralised Procedure, such procedure is not intended to be applied due to nature of MP - "over the counter" (OTC) authorised under the Centralised Procedure and, also, such a "switch" is less intended.(31)

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

**After the implementation of "Bolar**" provision in national legislation, the required testing can be done in the EU. This new provision may help to minimise the conduct of such trials by the generic industry outside the EU in 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 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 trial conducting necessary for the application for a generic marketing authorisation while the reference product was completely protected by a patent.

Initially, the Commission did not accept this claiming 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 was: "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". (42)

In real life, at least part of the two years of earlier generic submission before expiration of market exclusivity 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 are in force in late 2005 provide a serious 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 market exclusivity existing 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 become authorised after November 2005, in accordance with the formula "8+2+1" the first generic requests could only be submitted at the end of 2013. (31)

Additionally, there is no obligation the reference medicinal product to be on the market, no 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 MP (see Table 2). (31, 41, 42)

**Simplified procedure for herbal medicines introduces a new** category of herbal medicine based on traditional use and safety and quality should be shown like the 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 cosmetic 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 homeopathic medicinal products and Member States should take into account MAs that have been granted in other MS when evaluating an application. (13)

Commencing trials of the reference product before patent expiry will give the generic industry the opportunity to prepare the MP dossier much earlier. This may help to save cost and time in order to bring the MP quicker to the market. Even though the changes in the review of the pharmaceutical legislation 2005 provide many advantages for the generic industry for faster reaching the market, some critical legal issues are still left open. One of them is the lack of clear statute for the availability of official information relating to data exclusivity periods and patent issues of the reference medicinal products. On the other hand, it can be expected that 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. In the EU, only EMEA register for MPs under CP provides such information. (35)

The new EMEA Herbal Medicinal Product Committee will be 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 will support 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 a arbitration process in cases where mutual recognition procedure between the EU MSs could not be finalized successfully. The HMPC will also give confidence to the manufacturers in the area to submit applications. (97, 98)

**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 tthemselves 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 reform in 2005 is designed to yield concrete benefits for European consumers and patient in a rapidly changing world of the scientific field of the medicine. The Review focuses in reinforcing the proven success of EMEA set up in 1995. The important attempts are focused to optimise, rationalise and shorten the current regulatory processes, without changing the principle of the existing centralised and decentralised structure.

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. New legislation from 2005 will provide 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 period is being harmonised with the period provided for the centralised authorised MP**:** eight years data exclusivity and ten years market exclusivity.
- 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.

**Susses 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.
- Orphan designation now fall under the mandatory scope of the CP with the main idea all EU patient who need them to benefit from them.
- Concerning the duration of the assessment in the **Centralised Procedure**, the current deadline of 210 days could be reduced to 150 (28%) days in case of Accelerated Procedure for products of significant therapeutic interest.
- The Community Decision time in Review 2005 compared with the old legislation is decreased by 36 days.
- The time for the Community Decision is fixed to 15 days, which was not explicitly fixed in the previous EU Pharma law.
- 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 Accelerated Procedure within 217 days.

**Success in the Decentralised system of MA**

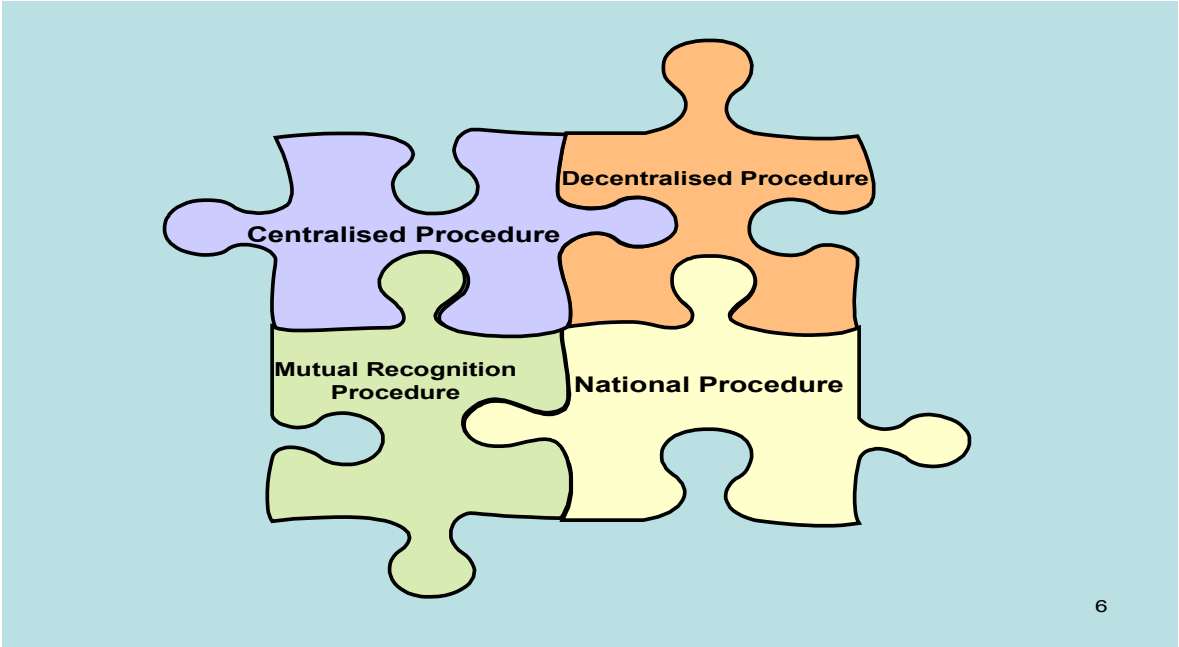
- The Mutual Recognition Procedure is being facilitated by introducing different modalities: Decentralised Procedure within 240 days, shorter by 180 (42%) days than the MRP (420) days depending on whether or not the medicinal product is already authorised in a MS.
- A future Guideline on the concept of "Potential serious risk for public health" will be introduced in order to clarify the MSs public health objection.
- CMD (h) Group, successor to the previous MRFG, is introduced with a legislative status. One of the objectives of CMD 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 should be developed).

**Success in Herbal and Homeopathic MP**

- **Simplified Registration Procedure** for certain homeopathic and traditional medicinal products is being 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 authorisations, National, Mutual, Decentralised and Centralised and the different specific, temporary, or accelerated procedures the patient in the enlarged EU with 25 and foreseen 27 countries in 2007 will be apparently assured with the needed medicinal products. Nevertheless the implementation of all new and updated approval procedures for MPs will be connected with many challenges and long term evolution. The various marketing authorisations (See Fig 7) are tools of choice for the applicant, except in the optional cases and they are add up to each other like a puzzle build up by the innovative and generic industry in order the EU market to be covered with all necessary, safe, qualified and effective medicines

**Figure 7. Marketing Authorisations Procedures in the EU**



In the EMEA Road Map to 2010 are summarised all current challenges in the pharmaceutical field, which could be faced like available limited 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 are summarised The EU regulatory system will be confronted over the years with significant changes of a legislative impact on the new Community legislation and institutional impact of the enlargement of the EU nature. In addition to these significant challenges having an impact on the overall system, other developing factors, which are nonetheless important, will have to be taken into account like continuation of the EU enlargement after 2004 with Romania and Bulgaria in 2007/2008 and other countries such as Turkey also seeking membership. (24)

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.

# 6. Summary

The marketing authorisation procedures for medicines 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 three separate procedures for receiving a marketing authorisation for a medicinal product: centralised, decentralised, and 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 provided the **Mutual Recognition Procedure (MRP)**, which had been introduced on the basis of Council Directive 93/39. For situations where an applicant intends to market the medicinal product in one Member State (MS) only, there is still the option to apply for a solely National Marketing Authorisation in this 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 from October 30, 2005 and introduced the Simplified Procedure for herbal and homeopathic MPs and the new Decentralised Procedure.

**The aim of this that study is to survey the EU pharmaceutical legislative frame of the intellectual 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 the comparative analyses provide many advantages that have been introduced in the new review 2005 versus former pharma legislation. The new legislation makes easier both innovative and generics products to access the European Market. It brings especially substantial improvements in the generics and innovative area in particular of introducing many new terms and issues: definition of generic, of reference medicinal products, of biosimilar.

Harmonisation of the 10-year market exclusivity period is introduced in the EU Pharma law. The new periods of the 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 market exclusivity 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.

Even the scope of the **Community procedure** is enlarged with many new diseases like acquired immune deficiency syndrome, cancer, diabetes, neurodegenerative disorders. Possibility for marketing authorisation of generic versions of a reference product authorised by the Centralised Procedure through the Mutual Recognition Procedure will be available. Biosimilar and orphan MPs are only in the scope of the Centralised Procedure in order the patients in all Member States to benefit from these products.

The legislative pharmaceutical documents, in force since autumn 2005, are focused on **Centralised accelerated assessment procedures** (217 days), which is by 60 days (28%)

shorter than the normal current CP (277 days). Concerning the duration of the assessment in the CP, the current deadline of 210 days **could be reduced up to 150 (22%)** days in case of Accelerated Procedure. The period till the Commission Decision (CD) becomes 36 (12%) days shorter than in the previous legislation. Now the time for Commission Decision is absolutely fixed, 15 days, in contrast with the previous legislation, where that period of time was not limited and legislatively fixed.

Except the specific marketing authorisation of medicinal products on Exceptional circumstances in force in the previous Community law, new temporary marketing authorisation **Conditional Authorisation and Compassionate use** with incomplete dossiers with positive risk/benefit balance, based on early evidence and annual reassessment for a rapid availability of innovative medicines for patients, are already possible.

In the newly established **Decentralised Procedure (DP)** the applicant is again free to choose the EU Member State that will act as the Reference Member State (RMS). Harmonisation in both procedures – DP/MRP, concerning Summary 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 with 180 (42%) days in the Referent Member State (RMS) and Concern 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)) Group in case of reaching consensus in 60 days. The new updated MRP, where claims of "potential serious risk to public health" are raised, will also profit in the same way from the new activity of the established CMD (h) Group, which replaces the Mutual Recognition Facilitating Group (MRFG).

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 Product Committee** will be 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 herbal medicinal product. 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.

In general, in Review 2005 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. Thanks to the network and the activities between the EMEA and 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.

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