

**Marketing Authorisation Procedures under the New  
Medicines Legislation – Impact on the Pharmaceutical  
Research Industry and Strategic Aspects**

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**List of Abbreviations**

AR	Assessment Report
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BPI	Bundesverband der Pharmazeutischen Industrie e.V.
CA	Competent Authority
CD	Commission Decision
CG	Co-ordination Group
CHMP	Committee for Medicinal Products for Human Use
CMS	Concerned Member State
COMP	Committee for Orphan Medicinal Products
CP	Centralised Procedure
CVMP	Committee for Medicinal Products for Veterinary Use
DCP	Decentralised Procedure
EC	European Commission
EFPIA	European Federation Of Pharmaceutical Industries And Associations
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FAR	Final Assessment Report
GMP	Good Manufacturing Practice
HMPC	Committee for Herbal Medicinal Products
INN	International Nonproprietary Name
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure
NtA	Notice to Applicants
OTC	Over-The-Counter
PAR	Preliminary Assessment Report
PIQ	Product Information Quality Review Group
PIL	Patient Information Leaflet
PIM	Product Information Management
PSUR	Periodic Safety Update Report
QRD	Quality Review of Documents Group
RMS	Reference Member State
RSI	Request for Supplementary Information
SAG	Scientific Advisory Group
SAWP	Scientific Advice Working Party
SMEs	Small and Medium-sized Enterprises
SmPC	Summary of Product Characteristics
TAG	Temporary Advisory Group
TOPRA	The Organisation of Professionals in Regulatory Affairs
VFA	Verband Forschender Arzneimittelhersteller e.V.
WHO	World Health Organisation

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# 1 Introduction

Following the review of the Pharmaceutical Legislation two legal rules applying to medicinal products for human use, i.e. Regulation 726/2004/EC<sup>1</sup> and Directive 2004/27/EC<sup>2</sup> were published in the Official Journal of the European Union on 30 April 2004. Regulation 726/2004/EC replaces Regulation 2309/93/EC<sup>3</sup>. Title IV covering the responsibilities and administrative structure of the European Medicines Agency (EMA) took effect on 20 May 2004 to allow for the Committees and Management Board to operate in the enlarged Europe. Remaining titles (I, II, III, V) including changes to the centralised procedure (CP) will come into effect on 20 November 2005. Two provisions of the Annex will be effective 20 May 2008. Directive 2004/27/EC amends Directive 2001/83/EC (further named Directive 2001/83/EC<sub>a</sub>) covering changes to the national and mutual recognition procedure which must be implemented in all European Member States (MSs) 18 months later by 31 October 2005. In addition Directive 2001/83/EC has been amended by Directives 2003/63/EC<sup>4</sup> (Annex I) and 2004/24/EC<sup>5</sup> (Herbals).

During the current transition period items are interpreted and transposed into national law in accordance with the New Medicines Legislation (NML) to enable smooth implementation in the best possible way and considering the interests of all parties involved, i.e. the EU Commission (EC), Competent Authorities (CA), The European Medicines Agency (EMA), pharmaceutical industry, generic industry, press and trade associations. To address these issues several events took place, e.g. the recent Conference on New Medicines Legislation in Brussels, October 2004, organised by The Organisation of Professionals in Regulatory Affairs (TOPRA) involving representatives from the main stakeholders.

There are still many issues to be addressed and clarified to achieve an effective and successful cooperation of all parties in order to strengthen the European Single Market. Mr. Philippe Brunet (Ex-Head of Unit European Commission, Enterprise DG, Pharmaceuticals. Regulatory Framework and Marketing Authorisations) noted that in the past there has been a more or less passive approach from Regulatory Authorities considered to have reacted to events and a regulatory system that puts the onus of product development on industry. Today a proactive approach is needed through a greater involvement of the Regulatory Authorities by way of earlier discussions on scientific and regulatory issues not just until granting of marketing authorisation (MA) but throughout the whole product life cycle<sup>6</sup>.

As the review of the NML provides many changes in different areas, this thesis will mainly concentrate on the outline of the major changes – provided by Directive 2001/83/EC<sub>a</sub> and Regulation 726/2004/EC - with respect to marketing authorisation procedures for medicinal products for human use, briefly providing a short overview about the history of the Pharmaceutical Legislation review and a summary of the major goals. It finally considers the implications of these changes on pharmaceutical research industry and suggests criteria for the selection of the most appropriate MA procedure. Reference is provided for more detailed information about the other changes addressed by the review report.

Each reference to articles of the NML is specified by either “D” for Directive 2001/83/EC<sup>a</sup> or “R” for Regulation 726/2004/EC.

It needs to be noted that for preparation of this thesis relevant information published until 26 April 2005 has been considered.

## **2 The History of the New Medicines Legislation**

On 1 January 1995 new community procedures concerning the authorisation and surveillance of medicinal products came into force and were implemented with a transition period until 31 December 1997: the centralised procedure (CP) which is currently mandatory for all biotechnology products (“Part A products”)<sup>3</sup> to acquire a single marketing authorisation which is valid for all EU Member States (MSs) following a scientific evaluation by the EMEA and a mutual recognition procedure (MRP) for national authorisations which is mandatory whenever an application for marketing authorisation for a medicinal product – not falling within Part A of the Annex<sup>3</sup> - concerns more than one EU Member State<sup>7</sup>. The EMEA plays a key role in this system by pooling the scientific expertise of all EU MSs in order to ensure a high level of public health protection and a free movement of pharmaceuticals.

Now both the international and European environment have been changed in particular the state of the art, i.e. new therapies are under development. Therefore the existing legislation must be carefully reviewed and adapted providing marketing authorisations covering practical and medical needs and fulfilling the major targets of the NML. On the basis of article 71 of Regulation 2309/93/EC “Within six years of the entry into force of this Regulation, the European Commission (EC) shall publish a general report on the experience acquired as a result of the operation of the procedures laid down in this regulation, in Chapter III of Directive 75/319/EEC and in Chapter IV of Directive 81/851/EEC”, in November 2001 the EC issued proposals for modifying the existing Pharmaceutical Legislation. These proposals are published in a report called “Review 2001” and based on an evaluation carried out by an independent consultant, i.e. Cameron McKenna and Anderson Consulting<sup>8</sup>. This approach aimed to guarantee a comprehensive and objective picture of the experience with the current marketing authorisation procedures made by all parties concerned such as the national authorities, industry, patients and health professionals.

The proposed legislation provided by the EC was finally adopted via a Co-Decision procedure by the European Parliament (EP) and the European Council, the two additional main „key drivers“ of the NML.

## **3 Major Goals and Changes**

The review of the Pharmaceutical Legislation has five major goals based on the report from Cameron McKenna and Anderson and adopted by the EC<sup>9</sup>, i.e. to:

- ensure a high level of public health
- strengthen the European Single Market
- provide transparency
- increase competitiveness
- prepare the EU enlargement

The following sub-chapters briefly summarise the measures which have been taken to achieve the major tasks described above<sup>10</sup>. The allocation of measures to the individual goals should be regarded as subjective as many measures contribute to all of them.

### **3.1 High Level of Public Health**

To guarantee European citizens a high level of health protection was one important objective of the review, in particular by making safe and innovative medicinal products available to patients as quickly as possible. Focus should be made on currently still unmet needs of patients, i.e. life-threatening conditions or illnesses. Therefore to simplify the current procedures was a further issue to achieve. Medicinal products offering a major innovation will benefit from a “fast track” centralised procedure similar to those already implemented in Japan<sup>11</sup> and the US<sup>12</sup>. The accelerated review will take 150 days (article 14 R). Further, a framework to allow prescription on a compassionate use basis will be put in place as laid down by article 83 of Regulation 726/2004/EC. Further changes affecting the centralised procedure allow a conditional authorisation for treatments intended for life-threatening, chronic or debilitating conditions, to be granted within one-year validity period (article 14 (7) R). In addition the scope of the CP has been widened as laid down in the Annex (R) (Chapter 5.2).

Modifications refer to general packaging (articles 54, 56a, 59 D), e.g. providing a new requirement regarding the use of Braille and a requirement that labelling and Patient Information Leaflet (PIL) will be addressed in the national marketing authorisation procedures (article 28 D) (Chapter 5.1.3).

The effects of the NML in relation to pharmacovigilance have been recently described<sup>13</sup>. For drug safety pharmacovigilance procedures have been strengthened throughout the lifecycle of the medicinal product given them a priority role independent from the nature of the product (article 26 R). A marketing authorisation needs to be renewed only once after five years (article 24 D, article 14 R), but as a consequence the Periodic Safety Update Report (PSUR) needs to be submitted on a three-year basis (currently five-year basis). In order that the risk-benefit ratio may be continuously assessed, the European Medicines Agency (EMA) may ask the MAH at any time to provide additional data that the risk-benefit ratio remains favourable (articles 16, 23 R). Upon request by the EMA, particularly in the context of pharmacovigilance, the MAH must provide all data relating to the sales volume within the Community separated for each MS and any data relating to the volume of prescriptions.

The definition of a medicinal product is extended taking into account new therapies (article 1 D).

The assessment of environmental risk needs to be submitted when applying for a MA (article 8 D)<sup>14,15</sup>.

Furthermore requirements for Good Manufacturing Practice (GMP) will be increased with respect to manufacturing of active substances, excipients, inspections, and certification (articles 46, 111, 122 D).

### **3.2 The European Single Market**

To strengthen the European Single Market, partitions with regard to different marketing authorisation procedures should be removed to lead to a “single European licensing system” applying the same criteria for evaluation<sup>6</sup>. However, under the NML the possibility to choose different MA routes has been maintained but several measures have been taken aiming on harmonisation. The Commission extended the scope of the centralised procedure taking into account some of the most important therapeutic needs of today and probably of the near future<sup>16</sup>. Various measures were taken to improve overall consistency of the CP (Chapter 5.2).

One purpose of the NML was to achieve a harmonised labelling - comparable to the labelling achieved through the CP - as in addition to the SmPC, the PIL and wording of the primary and secondary packaging will be part of the assessment through the “new” mutual recognition procedure (MRP) and decentralised procedure (DCP). Furthermore the structure and content of the PIL should be harmonised across the EU for medicinal products authorised through CP, MRP or DCP (article 59 D) (Chapter 5.1).

### **3.3 Transparency**

For transparency and public safety purposes the EMEA was asked to improve the transparency of the decision-making process.

Furthermore according to Regulation 726/2004/EC the following information contained in databases and documents held by the EMEA or Competent Authorities shall be made publicly available:

- the opinion of the Commission as referred to after disagreement through the MRP or DCP (article 5 (8))
- reasons for withdrawal of an application and the agency’s assessment report (article 11)
- information and reasons about all refusals (article 12 (3))
- the assessment report after granting a MA including its reasons. The European Public Assessment Report (EPAR) shall include a written summary covering also the conditions for use understandable to the public (article 13 (3))
- the list of obligations for granting a MA (article 14 (7))



- any urgent action taken and decision made by a MS for public health reasons (article 20 (4-7))
- agency opinions on measures concerning suspected adverse reactions (article 22 (1))
- any alerts taken relating to manufacturing or pharmacovigilance issues (article 26)
- information already authorised on PILs, SmPCs including a section for paediatric medicinal products and references on data on clinical trials (article 57)
- a register containing all documents that are publicly available (article 73)
- agency's internal rules and procedures (article 80)
- the names of the MAHs involved, the amounts of and reasons for penalties imposed (article 84 (3))
- to guarantee independence and transparency, staff of regulatory authorities, rapporteurs and experts responsible for granting a MA and surveillance of medicinal products must make an annual declaration of their financial interests (article 63 (2) R; article 126 b D).

Similar rules are laid down in Directive 2001/83/EC<sub>a</sub> (articles 21 (3, 4), 40 (4), 102 (2), 104 (9), 111 (6, 7), 125 (3), 126a/b).

### **3.4 Competitiveness**

The Commission set up a legal framework which fosters the competitiveness of the European industry. It was important to achieve the right balance between research and generic industry. Regarding research industry the Commission harmonised the regulatory data protection period for centralised and decentralised medicinal products at ten years across the board providing an essential element for a smoother operation of the single market. This period could be extended by one year when an innovative indication is granted within eight years after initial marketing authorisation. The outcome is the so-called "8+2+1 rule". This rule only applies to products for which marketing authorisation is granted after the new legislation came into force. The rest of the compromise on the data protection scheme and generic competition includes a one-year period in the case of switches from prescription medicines to Over-The-Counter (OTC) products (article 74 D) and a one-year period for well-established substances in the case of innovative indication (article 10 (5) D)<sup>16</sup>. The latter incentives will apply to line extensions submitted after November 2005, even if the product was approved under the current or "old" legislation. The "8+2+1" rule allows generic industry to apply for MA after eight years with market entry after 2 additional years (article 10 D, article 14 (11) R). For the first time a legal framework for biosimilar medicinal products has been developed and the legislation has been clarified regarding generics and the choice of the reference product, i.e. the reference product no longer has to be approved in the country where an application has been filed (article 10 (1) D). Thus in the future one MA of the original medicinal product (reference product) granted in the EU may be the basis for a generic MA application. In this case the applicant shall indicate in the application form the name of the MS in which the reference medicinal product is or has been authorised. Generic companies

have the option of either applying for the centralised or national authorisation procedure (article 3 (3) D). This breaks the current rule that an abridged application can be only submitted to an authority holding a copy of the original dossier. A „roche bolar“ rule will allow research and development (but not marketing) of a generic product before patent expiry (article 10 (6) D).

Due to the concept of a global marketing authorisation (article 6 D), there will be no additional data exclusivity for line extensions.

A marketing authorisation will become invalid if the product is not marketed within three years of authorisation or if a previously marketed product is not marketed for three consecutive years („Sunset Clause“, article 14 (4, 5) R, article 24 D).

### **3.5 EU Enlargement**

On 1 May 2004, ten new countries joined the EU. In order to be prepared for the EU enlargement, the EMEA underwent restructuring and its responsibility was increased (Chapter 4). In addition twinning programs as the principal tool of pre-accession assistance for new Member States have been established to help them in their development of modern and efficient administrations, with the structures, human resources and management skills needed to implement the NML to the same standards as the “old” Member States.<sup>17</sup>

Overall most of the changes described above can be considered as measures to be prepared for the involvement of the ten new MSs.

## **4 Consequences for the EMEA**

The EMEA was created in 1995 by Council Regulation 2309/93/EEC. The new Regulation 726/2004/EC replaced this Regulation. Elements of the new legislation that came into force in May 2004 include a consolidation of the agency’s international role and increased its role to handle all these tasks provided in Chapter 3. Adjustment is made in the sector of scientific advice to companies (article 56 R) – in particular for small and medium-sized companies (article 70 (2) R) – including fee reductions, exemptions and administrative assistance, cooperation with the World Health Organisation (WHO) in giving opinions for the use of medicines outside the EU (article 58 R), opinions on compassionate use of unapproved medicines in MSs, market surveillance, pharmacovigilance reporting including PSURs (articles 24 (2), (4) and 49 (2), (4), 55, 57) and public awareness of medicinal products (articles 78, 80 R). One mandate of the agency is the development of a database of all medicines approved in the EU (“EuroPharm”) according to the new Regulation (article 57 (2) R). Finally the EMEA will be responsible for financial penalties imposed by the EU Commission (article 84 (3) R).

The new name of the agency, European Medicines Agency, reflects its broader responsibility. The acronym 'EMA' continues to be used.

With respect to its administrative structure the Management Board and the Scientific Committees were affected, the changes include<sup>18</sup>:

- Committee for Medicinal Products for Human Use replaces the Committee for Proprietary Medicinal Products (CPMP). The new Committee is known as the CHMP (article 5 R). Membership of the Committee changed from two to one member plus one alternate per MS (following EU enlargement this means 25 members) and in addition one member from Iceland and Norway. The Committee may co-opt a maximum of five additional members (article 61 R).
- Committee for Medicinal Products for Veterinary Use replaces the Committee for Veterinary Medicinal Products. The new Committee continues to be known as the CVMP. Membership of the Committee is similar to the CHMP.
- There are no changes to the Committee for Orphan Medicinal Products (COMP).
- A new Committee for Herbal Medicinal Products was created known as the HMPC.
- Composition of the Management Board changed from two to one member per MS, in addition to two representatives each of the European Parliament and the European Commission. They are joined by two representatives of patient organisations, one representative of doctors' organisations and one representative of veterinarians' organisations. There are a total of 33 members of the Board (article 65 R).

## **5 Changes in the Marketing Authorisation Procedures**

### **5.1 The “New” Mutual Recognition Procedure & Decentralised Procedure**

Directive 2001/83/EC<sub>a</sub> contains essential changes in relation to mutual recognition and the possibility of obtaining marketing authorisation (MA) in several EU MSs. The new legislation describes two “national” marketing authorisation procedures: a new decentralised procedure (DCP) (article 28 (3) D) and a modified mutual recognition procedure (MRP) (article 28 (2) D). The major difference is that the DCP needs to be used for products where no MA has previously been granted whereas the MRP is only applicable for products with an existing MA in one or more MSs. Both procedures are available for all types of products (including homeopathic products according to article 16 (1)

D) except for those that are mandatory for CP. The initial assessment process (national phase) differs, whereas the subsequent European step is identical. Further details of both procedures are described below. It needs to be emphasised that the NML does not provide many details, thus requiring a close collaboration between the EU Commission, MSs, the Mutual Recognition Facilitation Group (MRFG) and preferably the pharmaceutical industry to establish further guidance for clarification. The information below should still be regarded as draft.

The operation of the current mutual recognition procedure<sup>19</sup> has been substantially improved since 1998, however, several aspects have been criticised and undergone review. The major aim was to improve the procedure's weak points and to reinforce its strong points. The main target for criticism of the current MRP was that MSs re-evaluate the complete authorisation application instead of "recognising" the Reference Member State's (RMS) Assessment Report<sup>9</sup>. Further if the first national authorisation seems to be not granted by a Concerned Member State (CMS) – which should result in a Community arbitration procedure (a referral after MRP or DCP is usually named "arbitration") – the applicant often withdrew the request for marketing authorisation in the MS concerned so providing no chance to resolve the dispute on a Community-wide level. The length of the arbitration procedure was also criticised. The reasons given raise to risk of public health are sometimes considered as inconsistent and difficult to understand. Reasons for this situation are seen in misusing the "serious risk to public health" concern by CMSs and though not recognising the assessment made by the RMS. Furthermore the MRFG has no legal basis and therefore its role during breakout sessions has only limited value<sup>10</sup>.

The main changes to both procedures, MRP and DCP, can be summarised as follows and are discussed in more detail in the subsequent chapters:

- a marketing authorisation needs to be renewed only once after 5 years and will be indefinite afterwards (currently the MA must be renewed every five years (article 24 D)
- only if regarded as necessary by the agency an assessment will be repeated after 5 years; for compensation increased pharmacovigilance requirements have been established
- MAs will expire where these are not put on the market for a continuous period of three years ("Sunset Clause")
- creation of a Co-ordination Group (CG) to facilitate agreement between MSs
- ability to market approved products in certain MSs although the procedure is still ongoing in other MSs
- for transparency, after granting a marketing authorisation, MSs must make the AR and SmPC publicly available together with the reason for their opinion, after deletion of any confidential information
- "in the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another MS"...a MS may for justified public health reasons authorise the placing on the market of the said medicinal product". This procedure increases the availability of the product, in particular to smaller countries (article 126a D)

- the concept of a “global marketing authorisation” has been introduced by the new Directive (article 6 D)
- for the Patient Information Leaflet readability testing needs to be performed (articles 61 (1), 63b (2), 59 (3) D)

It needs to be noted that the procedures described below should still be regarded as “draft” as discussions about the details are ongoing.

### **5.1.1 The “New” Mutual Recognition Procedure**

Where a national marketing authorisation is already granted by a MS's Competent Authority within 210 days as requested (article 17 (1) D) and the company intends to market the product in more than one MS (but does not use or cannot use the centralised procedure) the current and new legislation provides that the first national marketing authorisation should be recognised via the mutual recognition procedure (article 28 (2) D). The primary objective of the MRP is to avoid unnecessary duplicate effort during assessment of the marketing authorisation application (articles 17, 18 D). According to article 17 (2), MSs are now obliged to decline the assessment of an application if the application is already under review in another MS and must advise the applicant that the MRP has to be applied. Furthermore MSs have to reject an application if a marketing authorisation of this product in another MS already exists. The applicant will be forced to submit a new application for MRP (article 18 D).

A detailed and currently proposed flow chart of the “new” MRP is provided in Annex I.

The first Member State that granted MA (RMS = Reference Member State) prepares an Assessment Report (AR) within 90 days (article 28 (2) D) - covering any updates of the dossier filed in the meantime after MA - which is the basis for mutual recognition of the Concerned Member States (CMS). The NML now provides that the AR includes the finally approved SmPC, PIL and labelling. Up to this stage the procedure is still within the national phase.

In the subsequent European step the CMSs then have 90 days from the receipt of the AR and appended documentation and start of the procedure to either recognise the decision of the RMS including the SmPC, PIL and labelling or to provide comments for clarification or request for changes. In the latter case the applicant can submit its response package within ten days and in the case that some concerns still remain has the chance for an oral explanation during the Break-Out Session on Day 60. The total evaluation period of 90 days remains unchanged to the current MRP but it is proposed to shorten the time period for CMSs comments from 50 to 40 days which consequently will change all subsequent time points.

Currently it is understood that all the serious public health issues should be raised at Day 40 allowing sufficient time to resolve the issues until Day 90. If the issue cannot be solved until Day 90 due to disagreement between the MSs regarding the assessment of the medicinal product, i.e. one or more

CMSs consider that the current MA presents a risk to public health, the matter of concerns is raised to the Co-ordination Group (CG, article 29 (1) D). Directive 2001/83/EC<sub>a</sub> defines “a serious risk to public health” as “any risk relating to the quality, safety or efficacy of the medicinal product as regard to patients’ health or public health”. For an effective running of the procedure it is a prerequisite to define the term in more detail (article 29 (2) D). The Commission recently published a proposal for a “Guideline on the definition of a potential serious risk to public health”<sup>20</sup>. So far it is still unclear who will refer the case to the CG, the RMS or CMS. It is the purpose of the CG to reach agreement between all CMSs and to come to a final position within 60 days. During this stage the applicant is allowed to provide comments orally or in writing.

If CMSs could not reach agreement during the CG discussion phase, a CMS can apply for arbitration (referral) and a scientific evaluation of this issue is carried out by the CHMP of the EMEA. This procedure as laid down in articles 32-34 of Directive 2001/83/EC<sub>a</sub> leads to a single decision which is binding to all relevant Member States (arbitration or referral acc. article 29 D). Clarification is still needed to define who will trigger the arbitration in the case of a withdrawal, whether it would be the CMS where the application is withdrawn or the RMS or the CG.

In those cases where an arbitration is initiated, the NML provides that those MSs which obtained approval for granting a marketing authorisation are allowed to put the product on the market without waiting for the outcome of the arbitration procedure (article 29 (6) D). It is still unknown if more cases are referred for arbitration, although the applicant has withdrawn who will pay the fees. Nevertheless as soon as the Commission Decision (CD) has been issued, MSs which already put the product on the market, have to take all measures to adapt their marketing authorisation to the CD within 30 days after its notification (article 34 (3) D). Further the legislation provides that the CD reached after the arbitration procedure shall be addressed to all MSs (currently to the MSs concerned and MAH/applicant). It shall only be “reported for information” to the MAH or applicant. As a consequence also MSs which have not been involved in the arbitration procedure will have to comply with the CD once a marketing authorisation application is submitted to their Competent Authority. However the MAH or applicant still has the right to institute proceedings against the CD<sup>21</sup>.

In general a withdrawal of the marketing authorisation application in one or more MSs is possible at any time, i.e. during the national phase (*before* Day 210) or during the European assessment. It is currently understood that if the application is withdrawn until Day 119 a subsequent discussion of MSs’ concerns is not triggered thus there is no risk for arbitration. However in case of withdrawal during the European phase it needs to be considered that the CMS where the application is withdrawn due to serious risk to public health concerns will still bring forward the point for disagreement to the CG. If agreement could be reached and the CMS is satisfied a Repeat-Use procedure could be initiated to include the CMS again<sup>22</sup>.

The timetable of the procedure is in total approximately 420 days, i.e. 210 days (1<sup>st</sup> MA) plus 90 days (RMS AR) plus 90 days (European step) followed by the 30-day phase of national marketing authorisation. In case the CG needs to be involved the total procedure takes about 480 days.

### **5.1.2 The Decentralised Procedure**

The decentralised procedure (DCP) applies to products which were not previously authorised in any MS (article 28 (3) D). A final draft of the procedure, adopted as internal working document of the MRFG, is given in Annex II. Where the medicinal product has not received a marketing authorisation at the time of application, the applicant shall simultaneously submit the dossier to the RMS and CMSs and request the RMS to prepare a draft AR, a draft SmPC and a draft of the labelling and PIL within 120 days after receipt of a valid application (article 28 D). Prior to submission the applicant will have the opportunity to discuss with the RMS whether readability testing may be necessary or an expert justification can be provided instead, thus the main responsibility regarding PIL assessment is with the RMS. This issue will also be part of the Preliminary Assessment Report (PAR)<sup>23</sup>. The current proposal foresees that within this 120-day period the RMS forwards the PAR to all CMSs and the applicant on Day 85. On day 118 the CMSs need to provide their comments on the dossier, PAR and proposed SmPC (not on PIL and labelling at that stage) including potential serious risks to public health and potential disagreement with the RMS' position on the need for readability testing.<sup>23</sup> Afterwards a clock-off period about 30 days for preparation of a response package is currently proposed<sup>23</sup>. Taking into account the applicant's response the RMS shall send within 60 days after receipt of the applicant's response the draft AR, SmPC, PIL and labelling to the CMSs and the applicant on Day 120 when the clock restarts. This "national" step is followed by the European step as described in Chapter 5.1.1 during which the CMSs shall approve these documents accordingly within a 90-day procedure. In case a Break-Out Session will take place the RMS will circulate the meeting minutes to the Coordination Group, the CMSs and the applicant.<sup>23</sup> The RMS distributes the overall agreement to all parties involved and closes the procedure.

If within the 90-day period one or more CMS cannot adopt the draft documents provided by the RMS due to reasons of potential serious risk to public health, the respective CMS should provide detailed reasons for its position to all parties involved. The grounds for refusal, i.e. serious risk for public health, must be the same for MRP and DCP. The points of disagreement will then be referred to the CG (article 29 D) as described above (Chapter 5.1.1).

Analogue to the MRP, in those cases where the CMSs fail to reach an agreement within the CG discussion, the EMEA will be immediately informed about the initiation of an arbitration procedure (article 32 D). Also the considerations relating to a withdrawal apply (Chapter 5.1.1).

The total duration of the DCP without clock-stop is 210 days (article 17 D). Afterwards each MS should adopt the final decision and grant a national marketing authorisation within 30 days. The assessment process will be prolonged if the CG needs to be involved resulting in a total of 300 days. Considering the maximum time for the clock-off period the procedure lasts approximately 420 days.

Important differences to the MRP are that there is no marketing authorisation in the RMS at the beginning, that both, the RMS and the CMSs, are chosen before the first step of the procedure, and the timetable varies slightly (see Annex I + II). The MRFG will publish exact implementation details on its website.

### 5.1.3 Labelling

The introduction of the new DCP and the revision of the MRP intend to achieve an EU-wide harmonisation of the SmPC, PIL and labelling. As some national requirements for the outer packaging still remain, a “Blue Box” already known from centralised products needs to be implemented.

Furthermore, as stipulated by the NML the structure and content of the PIL should be harmonised across the EU for medicinal products authorised through CP, MRP or DCP (article 59 D). For example, in the PIL new information should be provided such as a list of the names of the medicinal product authorised in each MS. Further, patients are asked to consult the physician or pharmacist for any clarification on the products’ use (article 63b (2) D).

Article 56a requires that Braille is provided on the packaging. Furthermore patient information leaflets should be made available in formats for the blind (e.g. audio tape spoken) and partially sighted (article 56a D). The European Commission recently published the “Guidance concerning the Braille requirements for labelling and the package leaflet”<sup>24</sup>. It provides that article 56a will apply after 30 October 2005 to all medicinal products for which MA applications are submitted after this date. It is up to the company to include the Braille also on already authorised products. As Braille differs from country to country it is proposed to follow the “Marburger” standard. The name of the medicinal product followed by its strength (if more than one strength) should be put in Braille on the outer/secondary package. There is no need for Braille on the packaging of products or pack sizes which are only used in hospitals or administered by medically trained personnel only.

The applicant needs to provide all translations for the labelling at the beginning and at the end of the procedure. Companies that delay the 30-day timescale for national approval by not providing the labelling translations immediately after Day 90 may obtain penalties<sup>25</sup>.

Readability testing<sup>26</sup> needs to be performed in accordance with articles 61 (1), 63b (2) and 59 (3) D. Further guidance on the timing of readability testing in particular when the leaflet changes during the assessment, on the applicability,



methodology and transition period for already approved products, is still required.

For medicinal products authorised through the MRP or DCP, the same standards established by the Quality Review Documents Group (QRD) should be used as for CP.

Where the product contains up to three active substances, now the primary and secondary (outer) packaging must mention the international non-proprietary name (INN) (article 54a D).

#### **5.1.4 Role of the Co-ordination Group**

The current MRFG has no legal basis therefore decisions made in that group have only limited value. To improve the cooperation process between MSs a Co-ordination Group (CG) has been established to settle any disagreement during the MRP or DCP<sup>27</sup> as already described in Chapter 5.1.1 and 5.1.2 (latest news indicate that this group will be named “Co-ordination Group for Mutual Recognition and Decentralised Procedure” (CMD) in the near future). As stipulated in article 29 (4) of Directive 2001/83/EC<sub>a</sub> “if the MSs fail to reach agreement within the 60-day period laid down in paragraph 3, the agency shall be immediately informed,...”. Thus it could be concluded that an initiation by either the RMS or CMSs is not necessary anymore, it will finally be the responsibility of the CG to trigger a referral in such cases. With this respect further clarification is required.

The Co-ordination Group is legalised by articles 27-32 of Directive 2001/83/EC<sub>a</sub> and replaces the current MRFG. The CG is responsible for the examination of “any question relating to the marketing authorisation of a medicinal product in two or more MSs”.

The EMEA provides the secretariat for the Co-ordination Group. The CG is composed of one representative from each Member State, appointed for a renewable period of three years. Members could be accompanied by experts. The group must establish its own rule for procedure which needs to be accepted by the Commission and to make publicly available.

The tasks of the CG have been widened - ranging from procedural to regulatory and scientific work - compared to those fulfilled by the MRFG before. For purposes of harmonisation Member States are asked to forward to the CG a list of products identified for SmPC harmonisation on a yearly basis (article 30 D). This list will be forwarded to the Commission and then either the Commission or a Member State could initiate any action on harmonisation, e.g. an article 30 referral. Consequently the harmonisation process for existing marketing authorisations is accelerated by the CG<sup>21</sup>.

Currently the rules for the procedure are discussed by the MRFG and will become official after approval by the Commission. The CG will be operational from November 2005 but it is envisaged that it will start operating as the old MRFG with CG members from April 2005.

### 5.1.5 Referral Procedures

Referral procedures could be initiated according to articles 29 (arbitration after MRP/DCP), 30, 31, 35, 36 and 37 of Directive 2001/83/EC<sub>a</sub>. The procedures summarised in Table 1 differ basically in their purpose for use, the number of Rapporteur/Co-rapporteur involved, the initiator and the reason for initiation<sup>28</sup>. With regard to referrals to the CHMP, changes providing an improved procedure have been made in particular for procedures relating to an entire therapeutic class or to all medicinal products containing the same active substance.

The time period for the CHMP opinion is reduced from 90 days to 60 days (article 32 D).

Within 15 days after receipt of the opinion the applicant or MAH may raise objections against the opinion. In this case he shall forward a detailed justification to the EMEA within 60 days after receipt of the opinion. The EMEA must forward the final opinion to the applicant or MAH, Member States and the Commission within 15 days (currently 30 days). Both the EU Commission draft decision and final Commission Decision need to be prepared within 15 days (currently 30 days).

All these measures intent to speed up and facilitate the decision-making and the harmonisation process.

A flow-chart demonstrating the referral procedure and appeal process is provided in Annex III.

Table 1: Differences in the EU Referral Procedures

Procedure acc. Directive 2001/83/EC <sub>a</sub>	Purpose for Use	Number Rapporteur/ Co-rapp.	Initiator	Reason/Justification
<b>Article 29</b>	MRP/DCP	1/1	CMS	Disagreement in CMS („risk to public health“)
<b>Article 30</b>	Divergent decision	More than 1	MS, EC, MAH/ applicant	Harmonisation of divergent national decisions
<b>Article 31</b>	Community interest; class referrals	More than 1	MS, EC, MAH/ applicant	Harmonisation of divergent national decisions (focus on pharmacovigilance)
<b>Articles 35,36,37</b>	„Follow-up“ (PSUR, variation)	1/1	MS, MAH/ applicant	Harmonisation of national decisions <u>after</u> harmonisation of MA

## **5.2 The Centralised Procedure**

A marketing authorisation granted following an application via the centralised procedure (CP) follows a single scientific assessment of quality, efficacy and safety by the EMEA and involves cooperation between MSs and the European Commission<sup>29</sup>. Within the EMEA the CHMP is responsible for providing an opinion on any questions relating to the admissibility of the information submitted and the granting of the medicinal product.

According to the audit report the centralised procedure has successfully fulfilled its role.

The changes made to the centralised procedure take into account future development of science and technology as well as the enlargement of the EU. The main changes to the centralised procedure can be summarised as follows and are discussed in more details in the subsequent chapters:

- medicines are available on a compassionate use basis
- accelerated assessment procedures for products of major therapeutic interest are established
- an increased scope to include generic and OTC products
- compulsory for orphan medicinal products, products for new active compounds for treating AIDS, cancer, neurodegenerative disorders or diabetes
- reduction or deferral of fees, scientific advice for small and medium size enterprises (SMEs)
- increased transparency and availability of information to the general public
- a shortening of the decision-making process

However the general principles of the procedure are maintained.

### **5.2.1 Scope**

The CP is currently mandatory for all medicinal products resulting from biotechnology ("Part A products"), and optional for all new products, i.e. those containing an active substance not used in medicinal products placed on the market prior to January 1, 1995, or for innovative products ("Part B products")<sup>3</sup>. According to "Review 2001" access to the CP has been significantly widened. The CP will be compulsory for all new medicinal products defined in the Annex to the Regulation. This includes besides biotech products (including generics), products for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes, as well as designated orphan medicinal products<sup>30</sup>. After four years (May 2008) this list will be extended to include auto-immune diseases and other immune dysfunctions and viral diseases (article 3 R). Further modifications to that list may be possible in agreement with the Council and Parliament.

The CP will be optional for new active substances to be used for other indications or for any significant innovations or products presenting a Community interest (article 3 R). Access to the CP is also facilitated for

medicinal products that are not innovative but may be of benefit to society or patients if authorised on a community level, e.g. products supplied without medical prescription (OTC). The new scope makes European evaluation based on pooling the best scientific skills from national agencies even more necessary and requires a well-established European network for successful collaboration. By using both, the national resources provided by the EU MSs and the necessary external experience (EMA list of experts), the EMA aims at ensuring a high quality evaluation.

### 5.2.2 Procedure

As currently practiced, the CHMP still needs to provide its opinion on the valid application after 210 days (article 6 R). According to the new requirement the duration of the assessment of the scientific data must be at least 80 days (article 6 R) instead of 70 days in the current procedure. Exceptions refer to those cases where Rapporteur and Co-rapporteur declare earlier completion of the assessment. The Co-rapporteur will develop into a new peer review role. The EMA recently published a Standard Operating Procedure (effective since 15 April 2005) applying to CHMP members assigned as peer reviewers, other CHMP members and EMA staff during the initial assessment phase to improve the quality of the Day 120 List of Questions (LoQ)<sup>31</sup>. Thus, where appropriate the CHMP can also send a request for supplementary information to the applicant within a set period. If this is the case the delivery of the opinion is suspended until the supplementary information is provided. Similarly the time periods will be suspended in cases of oral or written explanations by the applicant. A flow-chart of the major procedural steps is provided in Annex IV.

If the CHMP opinion reflects that the application does not satisfy the criteria for MA or the authorisation should be granted subject to condition, within 15 days after receipt of the opinion the applicant can provide written notice of its intention to appeal (Annex III). In addition the applicant must provide EMA with its detailed reasons for appeal within 60 days after receipt of the opinion. The final CHMP opinion is adopted within 60 days and forwarded to the Commission, Member States and applicant within 15 days after the adoption. Further details about the decision-making process are provided in Chapter 5.2.3.

The NML provides additional procedures under certain conditions, e.g. according to article 83 of Regulation 726/2004 compassionate use procedures for supplying unlicensed products will be formalised by a harmonised system.

Article 14 (8) 726/2004/EC provides that a MA may be granted subject to certain specific conditions and reviewed by the EMA on a yearly basis. The list of these obligations must be publicly available. The conditional authorisation may be valid for one year on a renewable basis. Further legislation to provide the conditions for conditional MA needs to be adopted. It is most likely that these rules apply to medicines for chronic/life-threatening diseases, orphan medicines and some others which still need to be defined.

Specific leaflet information requirements and specific PSUR reporting requirements are expected.

Currently another possibility for an early entry on the market is the MA under exceptional circumstances as defined in article 14 (R). This process allows the granting of a MA despite of lack of comprehensive data on quality, efficacy and safety. For clarification further guidance is needed.

When a MA application submitted is of major interest for public health issues, e.g. a therapeutic innovation, the applicant may apply with justified grounds for an accelerated procedure or fast track procedure (article 14 (9) R). If accepted by the CHMP the time limit for the opinion is reduced from 210 days to 150 days.

Due to increasingly complex technologies and methodologies employed in drug development, the EMEA plans to develop areas of specialisation (“Centres of Excellence”) to facilitate the most effective and efficient use of expertise and resources across the European Competent Authorities<sup>32</sup>.

In general a withdrawal is possible at any time but it needs to be considered that this would automatically lead to a withdrawal in all MSs.

### **5.2.3 Decision-Making Process & Appeal Procedure**

The current Commission’s decision-making process<sup>33</sup> was one of the most criticised aspects. This process has sometimes required up to a third of the total time required for the entire authorisation procedure<sup>6</sup>. With the new legislation the process will be accelerated (Annex V). The agency will be required to provide the final CHMP opinion to the Commission within 15 days (currently 30 days) (article 9 R). Both the EU Commission draft decision and final Commission Decision annexed by a SmPC (= Annex I to the CD), conditions for authorisation (= Annex II to the CD) and text of labelling and patient information leaflet (= Annex III to the CD) need to be prepared within 15 days (currently 30 days). If Member States acting through the Standing Committee (qualified majority vote) have any comments to the draft decision they need to be provided to the Commission within 22 days (currently 28 days) (article 10 R). The new legislation stipulates that a written procedure should be used even if the Commission draft decision disagrees with the EMEA, thus providing a faster alternative to the currently often held plenary meetings.

The procedures (articles 72, 73 of Regulation 2309/93/EC) currently used by the Standing Committee to adopt a decision for MA have been changed. In the future, the MA decision will be adopted via the management procedure (article 87 (3) R), which means that if the Standing Committee rejects the draft decision and subsequently the matter is transferred to the Council, the Council only can reject the draft decision with a qualified majority (currently with a simplified majority). In addition now it is possible for the Council to adopt a different decision or for the Commission to resubmit an amended draft decision (currently in the case of rejection by the Council, the procedure ends in no decision). However, if important scientific or technical issues are raised

during the decision-making procedure, the regulatory committee procedure will be used as before<sup>34</sup>.

Within 15 days after receipt of the opinion the applicant or MAH may appeal against the opinion. In this case he shall forward a detailed justification to the EMEA within 60 days after receipt of the opinion. The EMEA must forward the final opinion to the applicant or MAH, Member States and the Commission within 15 days (currently 30 days). A scheme covering the steps of the appeal procedure is provided in Annex III.

When the MA is granted the assessment report as well as the reasons for its opinion must be published on the EMEA web site after deletion of any confidential information. The so-called EPAR (European Public Assessment Report) is available for any interested person.

Only one authorisation will be granted to a particular applicant for a specific medicinal product. Only in exceptional circumstances the Commission will allow more than one application from the same applicant for the same product (co-marketing) (article 82 R).

Obtaining a marketing authorisation through the CP including the decision-making process takes in total about 367 days (incl. clock-stop).

### **5.3 Expiry of the Marketing Authorisation**

There has been a certain perception that the renewals of marketing authorisation are less and less based in practice on a scientific re-evaluation, but appear to be a simple administrative procedure. This situation causes financial burdens to the marketing authorisation holders and is resource consuming for the Competent Authorities without adding to the protection of public health. Currently a marketing authorisation must be renewed every 5 years<sup>35,36</sup>. Article 24 of Directive 2001/83/EC<sub>a</sub> and article 14 of Regulation 726/2004/EC provide that a marketing authorisation should be renewed only once, i.e. five years after granting of the MA. The renewal is based on a re-evaluation of the risk-benefit ratio by the regulatory authority. For this purpose the MAH must provide the regulatory authority with a consolidated version of the marketing authorisation file in respect of quality, safety and efficacy, including all variations introduced since marketing authorisation was granted, at least six months (currently three months) before the marketing authorisation ceases to be valid. Thereafter the marketing authorisation should normally be of unlimited validity unless the regulatory authority decides for pharmacovigilance reasons to perform one additional five-year renewal.

The new pharmaceutical legislation introduces in addition the so-called "Sunset Clause" (article 24 (4), (5), (6) D) and article 14 (4), (5), (6) R), whereby any marketing authorisation not placed on the market for three consecutive years will cease to be valid. The reason behind is to reduce the administrative workload regarding products' maintenance. However, exemptions from this rule will be granted if justified on public health grounds. For this purpose after granting a marketing authorisation, the MAH must inform

the regulatory authority of the date of actual marketing of the medicinal product including the various presentations authorised. The regulatory authority must also be notified if the product ceases to be on the market, either temporarily or permanently. This notification must be made no less than two months before the interruption in the placing on the market of the product.

The Commission is to set up a publicly accessible register of medicinal products authorised by MSs including the name or corporate name and permanent address of the marketing authorisation holder.

## **6 Impact on Pharmaceutical Industry**

The implementation of the NML in particular Directive 2001/83/EC<sub>a</sub> requires an update of the national legislation. In Germany the draft proposal ("Regierungsentwurf") of the 14<sup>th</sup> amendment of the German Drug Law (14. Novellierung des Arzneimittelgesetzes) has been recently published<sup>37</sup>. The new national legislation must become effective 31 October 2005. The following sub-chapters outline the impact on the pharmaceutical research industry and the proposals foreseen by the revised German legislation.

### **6.1 Marketing Authorisation Procedures**

The European Federation Of Pharmaceutical Industries And Associations (EFPIA) supports the changes with respect to the MA procedures as it requested that "optionality" for a company in deciding the appropriate marketing authorisation procedure for new active substances must be maintained<sup>38</sup>. It has been emphasised that both procedures, the CP and MRP/DCP, should ensure the same high level of public health. However, to have products authorised more rapidly, only the time allowed for certain administrative tasks has been shortened.

The increased focus on pharmacovigilance would result in a higher workload and finally in an increased risk for label changes. The possibility of the Competent Authority to re-assess the marketing authorisation at any time would require an internal management plan of such spontaneous situations.

Reasons for withdrawal by the applicant, for refusal of the application or conditions for granting a marketing authorisation must be made publicly available (articles 11, 12, 14 (7) R, article 22 D), allowing a deeper insight in competitive products.

Concerning intellectual property the provision of additional regulatory data protection periods (Chapter 3.4) will help to maximise research and development activities for new indications and valuably contribute to public health. To extend the ten-year period to a maximum of eleven years the MAH needs to bring "...a significant clinical benefit in comparison to existing therapies..." (article 10 (1) D) whereas a lower hurdle is provided for an additional one-year data exclusivity for a new indication for well-established medicinal products. This will be granted "...provided that significant pre-clinical

or clinical studies were carried out...” (article 10 (5) D). The industry would have preferred one extra year of regulatory data protection - now it is maximum one extra year - for each new indication of significant clinical benefit to stipulate further research activities. As laid down in the draft 14<sup>th</sup> amendment to the German Drug Law, the new rules provided for data protection and market exclusivity have been nationally adopted and refer to reference products for which a marketing authorisation application has been submitted after 30 October 2005 (article 24)<sup>37</sup>.

### **6.1.1 The MRP/DCP**

With respect to the MRP/DCP the main issue raised by the pharmaceutical industry during the review process was the fact that currently no real mutual recognition process has been practiced. An aspect which still has not been considered for the new procedures.

EFPIA has been invited by the MRFG to carefully review the current proposals and to provide any comments for consideration within the next MRFG meetings. In their draft position paper dated 20 July 2004<sup>39</sup>, they raised several issues to be considered. In the existing MRP the CMSs' non-compliance with the timelines agreed in the MRFG Best Practice Guides<sup>40</sup> has been under criticism. There is still a concern that since MSs often do not adhere to the current 50-day timeline to provide their comments, it is questioned whether they will be able to adhere to the proposed 40-day timeline. To avoid that this may continue in the future and to ensure the effectiveness of the new procedures in particular during the Break-Out Sessions, it is regarded as appropriate to strengthen and formalise the role of the RMS as a co-ordinator. This could be achieved via revision of the MRFG Best Practice Guides and Notice to Applicants Volume 2A, Chapter 2. Furthermore, to avoid unnecessary automatic triggering of the CG phase due to unresolved concerns raised at the last minute of the 90-day procedure, a close collaboration with the CMSs to get any concerns resolved prior Day 90, should be one of the major tasks of the RMS. In its role as co-ordinator the RMS should ensure that all CMSs that raised concerns should attend the Break-Out Session to make the discussion more effective than present. In the case the concerns are referred to the CG it should be allowed to submit supplementary data or to prepare for an oral hearing if necessary to resolve the issues under discussion. The CG should support the RMS as much as possible in terms of opportunities for an oral explanation or timings and venues for meetings with the CMSs.

The TOPRA Conference discussed also the pros and cons of the MRP and DCP<sup>25</sup>. The most critical advantage is the freedom to choose the regulatory authorities. Additionally the possibility to withdraw and to launch across the EU was noted as advantages. Disadvantages included the inconsistent behaviour from the CMSs, poor predictability and the lack of substantial support from the EMEA. It was mentioned that it may be unlikely that the new DCP will be more effective or more competitive and there might be some risks, of, e.g. introducing a concertation-type procedure in the DCP with associated risk of no approvals and/or agreed SmPC. Currently it cannot be foreseen if the



revised MRP and new DCP will deliver a more effective or more competitive procedure. There is still a risk for a double standard and consistency as two parties, the CG and the CHMP, are involved in the discussion in case of disagreement.

Although the European step of the MRP/DCP still allows withdrawal of the application in case of serious public health concerns a large number of arbitrations (referrals) could be expected. Such referrals should be avoided or at least to be kept to a minimum to avoid that the CHMP is overloaded with arbitration procedures, thus it is of high importance to ensure that the 90-day procedure and the CG phase are used most effectively and properly. As the CMS where an application was withdrawn will still bring forward the point for disagreement to the CG and further to the CHMP if agreement could not be reached, the benefit of a withdrawal is questionable. If an agreement could be reached during the CG discussion satisfying the CMS the MAH would need to start a Repeat-Use procedure to include this MS again.

If arbitration is initiated, in principle the MAH can put the product on the market in those MSs which approved the label. But it could be questioned if the MS is willing to grant a MA or if it prefers to wait for the outcome of the arbitration. This may be issue driven, e.g. in case of a safety issue the CMSs would probably be reluctant to grant the licence.

Following the requirements laid down in article 29 (2), the European Commission recently published a draft guideline defining a potential serious risk to public health<sup>20</sup>. Future practice needs to show if the ground for a refusal will really be the same for MRP, DCP, CP and national MA applications.

The requirement for publication of agencies' opinions will be nationally implemented, which would permit more insight into exchanged communication between all national agencies involved during a MRP or DCP<sup>41</sup>. Information which should be made publicly available is provided in article 34 of the amended new German Drug Law. Article 77a includes measures to be taken by the Competent Authority and the Regional State Authority (Überwachungsbehörde) to prove their independency and make internal agendas, meeting reports and rules for procedures publicly available.

A conclusion has been drawn that revised article 116 (D) facilitates the possibility for a Competent Authority to suspend, revoke, withdraw or vary an existing MA<sup>32</sup>. However, the burden of proof for the facts to take these measures still exists, thus the CA needs to provide justified reasons for any such measures taken.

For the applicants the most interesting amendment will be the possibility of access to the mutual recognition procedure via DCP even without an existing MA in another MS and in addition rapidly receiving a MA in the approving CMSs even in case an arbitration procedure is triggered<sup>21</sup>.

In Germany the EU rules for both mutual recognition procedures (MRP and DCP) will be implemented via article 25b of the 14<sup>th</sup> amendment to the German Drug Law. In the future applicants will also benefit from the fact that

the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) accepts the English version of the application forms<sup>42</sup>.

### 6.1.2 The Centralised Procedure

In its draft position paper on the centralised procedure EFPIA summarised the key issues for the pharmaceutical industry<sup>43</sup>:

- establishment of a transparent and scientific assessment approach
- ongoing dialogue with the agency during drug development
- an optimised use of European resources
- a fast procedure
- consideration of commercialisation needs, i.e. co-marketing and co-promotion

Pharmaceutical companies will need to take account of the impact of the changes with respect to the widening of the access to the CP. This rule will affect the availability of medicinal products as well as marketing and pricing strategies. The therapeutic areas may raise problems for indications that do not clearly fit to one of these categories, especially where clear guidance is not available. On the other hand the revised Annex (R) provides several advantages. These types or classes of products (partly based on complex techniques, e.g. gene therapy) are of major relevance for public health and due to complexity require a decision based on the opinion of each EU Member State as presented by the CHMP. In particular pooling the best scientific skills from national agencies makes the decision-making process as effective as possible. Furthermore the applicant has still the chance that products not covered by the Annex (R) could be centrally approved if he is able to show that the product is significantly innovative and/or of community interest.

In addition the broadening in scope of the CP is expected to bring administrative savings to the pharmaceutical industry able to benefit from the single application procedure<sup>44</sup>. Finally the revision of the Annex to the Regulation EEC 2309/93 follows the principles of the *“acquis communautaire”*<sup>45</sup>.

As it is in the interest of the pharmaceutical industry to consult Competent Authorities at an early stage and take account of all sets of scientific and regulatory advice, focus on CP would reduce the communication possibilities with the local agency. The CP does not foresee any contact with the local agency. The current lack of openness and proper dialogue within the CP is a major concern. Furthermore, as the assessment process of the CHMP is still not transparent, transparency must be improved throughout the procedure. In order to respond to a question as effective as possible, it is very important for the applicant to understand who asked a question, why and under which circumstances the issue was raised<sup>43</sup>.

The exclusion of MA of new active compounds from certain areas from MRP could result in a monopoly and overload of the CP, hence in a reduction of the influence of the national regulatory authorities. This would also have an impact on the duration of Scientific Advice procedures as well as on the successful

and timely management of the evaluation of an MA application in case the EMEA capacity remains unchanged. Unfortunately EFPIA's major concern, the current lack of openness and proper dialogue within the CP between the EMEA, CHMP/experts and the applicant throughout the evaluation process, still remains as industry representatives are not welcomed on the new Management Board.

Currently, the Rapporteur and Co-rapporteur for a MA assessment are assigned by the CHMP on the basis of equal distribution of workload rather than the provision of adequate expertise and sometimes without considering the applicant's proposal. The new rules of procedure for the CHMP indicate that industry will be able to nominate but that Rapporteurs shall be appointed "on the basis of objective criteria, which will allow the use of the best available expertise in the EU on the relevant scientific area". These criteria are currently being elaborated and will result in changes to the current procedure in due course. An earlier appointment of the Rapporteur than currently would allow useful interactions with the company and help to reduce requests for supplementary information and clarifications on data<sup>43</sup>.

Changes regarding the appeal process are not provided by the NML. An appeal to the CHMP opinion is still heard and discussed by the same committee that provided the initial opinion. In this respect the CP offers less justice than the MRP/DCP where in case of disagreement a separate body, the CG, and finally the CHMP, is involved. EFPIA made proposals for improvement which unfortunately have not been considered<sup>43</sup>.

The establishment of the Scientific Advice Working Party (SAWP) is welcomed by the pharmaceutical industry to get a continuous and timely PAN-European advice supporting clinical development programs and supporting the CHMP in addressing the increasingly complex issues associated with drug development. A major request from industry is that the dialogue between the applicant and the same regulatory assessor should be encouraged to build agreement and common understanding over time. By this agency's resources could be used as much effective as possible.

To streamline the workload of the CHMP EFPIA supports the delegation of assessment work to experts from established therapeutic advisory groups (Temporary Working Parties (TAGs)/ Scientific Advisory Groups (SAGs)). The pharmaceutical Industry would welcome a transparent and efficient interaction with the Rapporteur, Co-rapporteur and SAG. Finally the early contribution of the SAG could increase the predictability of the regulatory outcome<sup>43</sup>.

Accelerated MA procedures as well as the shortening of the decision-making process ensure patients an earlier availability of the medicinal products. To comply with the proposed timelines would be a big challenge for the EMEA and the Commission in particular considering the increased number of languages as a result of the enlargement. The current proposal for the decision-making process includes the linguistic review process as well. This would delay the timely printing of all labelling materials and consequently the delay of the product launch. According to EFPIA the linguistic review process should be streamlined, e.g. by implementing the Product Information Management (PIM) project (the electronic exchange of documents between regulators and applicants) on time<sup>43</sup>. For this purpose EFPIA developed several proposals which should be considered<sup>46</sup>: the Commission should start

preparing the decision based on the English version; the review process should usefully begin prior final opinion; for QRD, Product Information Quality Review Group (PIQ) and Member States a consolidated review of Product Information is required; PIM should allow only review of amended sections; a combined SmPC and PIL for different strengths and presentations of the same product should be allowed; the requirement to provide specimens in each MS's language prior to launch should be removed.

The outcome of the TOPRA conference confirmed that the industry welcomed the shortened CP approval time frame but still requires measures to oblige national regulatory authorities to adhere to the time frames set down in Community legislation (Directive 2001/83/EC<sub>a</sub>) for reviewing MA applications. Further remarks also referred to the obligation to use the CP for innovative medicinal products leading to an increase of costs for translations of SmPCs and PILs into 20 or more official languages which could extremely impact smaller companies<sup>25</sup>.

EFPIA requires that the applicant should be consulted in case of negative Opinions prior to publication. In addition, EPARs should be updated immediately following the Commission Decision to provide rapid access to the public<sup>43</sup>.

As the CP provides one tradename only, the main issue of concern are the potential difficulties of getting approval for one single tradename. With the new MSs being part of the EU it is foreseen to be even more difficult to agree on one common tradename. Besides this the criteria for the evaluation of the proposed tradenames are still unknown. The pharmaceutical industry requests that exceptions to trademark rule should be possible and further defined. In addition the evaluation process should become more transparent and the possibility to appeal against a decision on tradenames should be provided.

The new Regulation states that multiple applications cannot be granted to an applicant for a specific medicinal product. However, EFPIA stipulates that the Commission shall allow the submission of more than one application for objective verifiable reasons relating to public health regarding the availability of the medicinal product to physicians and/or patients, or for co-marketing purposes. Regarding cooperation among European companies the same flexibility should be provided as stipulated in article 98 of Directive 2001/83/EC<sub>a</sub><sup>43</sup>.

Data protection will be the key for industry as generic products must not be marketed within a ten-year period. Regarding the enforcement of a two-year market exclusivity it remains to be clarified if this issue is up to industry. A control mechanism needs to be established to avoid the launch of a generic if it is already granted between year 8 and 10.

The new Regulation (article 83) primarily provides the principle of Compassionate use. It allows access to drugs reviewed via the CP for "patients with a chronically or serious debilitating disease, or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product" (article 83 (2) R). Unfortunately products

intended to be authorised via the national MA procedure are not covered. Nationally this principle will be implemented via article 21 of the 14<sup>th</sup> amendment of the German Drug Law (draft)<sup>37</sup> which mainly refers to the content of the regulation, thus further guidance will be required, e.g. who can initiate the program and who will make a decision.

Small and medium-sized companies will benefit from additional administrative support by the EMEA and reduced or deferred registration fees<sup>47</sup>. Financial penalties will be imposed on companies failing to meet their obligations and commitments under the new legislation<sup>48</sup>. Unfortunately similar measures in case of violation of the law by Competent Authorities are not foreseen.

Clarification is needed how to proceed with ongoing applications where the medicinal products are still under review when the deadline for implementation of the review is reached.

## **6.2 Labelling**

The Guidance concerning the Braille requirements recently published by the EC (Chapter 5.1.3) considered most of the comments raised by EFPIA and the German Industry Associations, BPI and VFA<sup>49,50,51,52</sup>. Clarification is required on the optional procedure to apply Braille to existing products. It is still EFPIA's concern that individual MSs demand additional and/or different Braille requirements which would be contrary to achieving an EU-wide packaging harmonisation. Finally the provision of the PIL for blind and partially sighted will become a big challenge for the pharmaceutical industry.

Furthermore with respect to readability testing, the applicability, the number of languages to be tested, the procedure and methodology are still open issues to be specified. The German associations propose that readability testing should not be generally binding for all products. Exceptions should be made for products using the standardised templates/core texts ("Musterpackungs-beilagen") from the BfArM and those which are solely administered by medically trained personnel<sup>42</sup>.

In Germany the requirements for Braille are clarified by the so-called "small" amendment to the German Drug Law ("Kleine AMG-Novelle")<sup>53</sup>. It is requested that the name of the medicinal product should be provided in Braille. The packaging of products or pack sizes which are only used in hospitals or administered by medically trained personnel are excluded from this requirement. The transition period has been extended in the way that medicinal products authorised before 30 October 2005, could be placed on the market without Braille until the next renewal or at least until 31 October 2007. For products without Braille already on the market, there is no deadline for selling<sup>54</sup>. For medicinal products approved after 30 October 2005 Braille needs to be implemented until 1 September 2006.

In the draft of the 14<sup>th</sup> amendment of the German Drug Law<sup>37</sup> the comprehensive changes regarding SmPC, PIL and labelling as provided by the Directive have been predominantly adopted and should be implemented prospectively (articles 10, 11, 11a). Except for Braille, currently transition

periods until 1 September 2007 (SmPC) and 1 September 2008 (PIL and labelling) are proposed which finally considered industry concerns<sup>55,42,52</sup>. For existing products it is currently unknown how to handle the implementation e.g. with future variations or renewals thus further clarification will be necessary<sup>52</sup>. Labelling harmonisation has been a major task for the NML but it could be questioned whether this will be really achieved in practice as the implementation of the European Directive is up to the national legislative thus allowing some national flexibility with respect to interpretation and final adoption of the European requirements. A varied experience from the past also provides reasons for concern.

### **6.3 Renewals & Sunset Clause**

Article 23 (D) gives the Competent Authority the right to continuously assess the risk-benefit balance at any time asking the MAH to forward data demonstrating that the risk-benefit ratio still remains favourable. EFPIA commented that the risk-benefit balance is regularly monitored and documented through the product's life-cycle<sup>56</sup>. Information is forwarded through the 15-day spontaneous report of individual cases of suspected serious adverse reactions and through the mandatory periodic safety update report (PSUR), pharmacovigilance measure which are to EFPIA's opinion properly addressed in the NTA Pharmacovigilance Guideline Volume 9<sup>55</sup>. Therefore the request for additional data to confirm a positive benefit-risk balance should only be done in exceptional cases which should be further defined.

In general EFPIA welcomes the introduction of only one five-year renewal. However, there should be no need for renewals where products have already been renewed for several times. It was stated by a pharmaceutical industry delegate that industry preferred to bring innovative products on the market rather than follow what seems to be a retrospective step of another renewal. To do already performed renewals again will take a lot of resources that could be best use for any other priorities<sup>25</sup>.

EFPIA does not agree to additional renewals requested by the CA if there are no serious pharmacovigilance concerns. If an additional assessment would become necessary this should be combined with the review of the routinely reported adverse reactions or PSURs. The need for a second renewal should be an exception and based on justified grounds. Furthermore situations where MSs have different opinions about the need for a second renewal still require clarification<sup>56</sup>.

The meaning of "a consolidated version of the file" (article 24 D) needs to be clarified to avoid validation failures. EFPIA proposed to allow the same format which was used for the original filing.

With respect to the Sunset Clause (article 14 (4, 5) R, article 24 D) the current proposal is that it will be sufficient to keep one pharmaceutical form or one pack size on the market to be no subject for loss of MA. However the MAH should be contacted prior invalidation to allow a justification of the reasons

why the product has not been used for three years. In addition criteria for an exemption “in exceptional circumstances and on public health grounds” should be clearly defined<sup>56</sup>.

The current draft of the 14<sup>th</sup> amendment of the German Drug Law<sup>37</sup> foresees that the new rules (article 31) for renewals directly apply when the new law will come into force with various transition periods to be considered as currently proposed in article 140. The current draft provides that for marketing authorisations renewed in the period between 1 January 2001 and the entry into force of the new law the BfArM may only ask for an additional renewal for justified reasons. Further, the application for renewal must be provided at least six months before the MA ceases to be valid (transition period proposed). The German Industry Association still proposes to exempt all products which have been renewed once<sup>52,57</sup>. It is argued that in return several measures have been taken, i.e. three-year interval for PSURs and the “Sunset Clause”<sup>42</sup>.

Regarding the period of three years defining the Sunset Clause it is interpreted that the period will start after coming into force of the amended German Drug Law, an assumption which still needs to be proved. Discussions are still ongoing about MAs which currently rest or for which resting has been applied<sup>52</sup> and MAs obtained for export purposes.

## **7 Strategic Aspects for the Selection of the Procedure**

With the NML companies are offered different options in pursuing marketing authorisations for their products. The new regulation has specified when a product must follow the centralised procedure and when this route is an option based on the nature of the medicinal product. Therefore the first step for defining a regulatory strategy should be a review of the Annex (R) to clarify if the CP would be mandatory or not. If the applicant is not forced to enter the CP the choice will be between the MRP/DCP and CP.

Besides the nature of the medicinal product, several factors may also have an impact on the selection of the MA route<sup>58</sup>. Important are e.g. issues relating to tradename, co-marketing/co-promotion, and the nature of the MA procedure. With the provisions of the NML, both, the data exclusivity period which has been harmonised to 10 years as well as the patent situation, will not be an issue for the pharmaceutical research industry.

Quite common the procedure is already predefined by the classification of the medicinal product. If both the national (MRP/DCP) and the centralised procedure are possible, the variety of criteria summarised in Table 2 indicate that besides “Regulatory Affairs” further departments, responsible for tradenames, patent and marketing should be involved in the decision-making process.

Positive aspects of the MRP/DCP include its high flexibility with regard to market selection, co-promotion/co-marketing activities, trademarks, and samples as well as time to market for the first MA granted by the RMS (the

latter refers to MRP only). The CP is less flexible than the MRP/DCP in terms of MAHs, trademarks, co-marketing, co-promotion and duplicate applications. Furthermore the EU enlargement brings even more complexity to the system, especially considering the differences in national requirements (legal status, pricing, reimbursement).

The MRP and DCP permit the use of different tradenames. It is common practice for European companies to build up co-marketing/co-promotion agreements with other companies. Co-marketing and co-promotional activities can be easily implemented through both mutual recognition procedures, i.e. allowing the parallel application for various clones of the “original” medicinal products. The European Commission does not accept more than one tradename for a MA license gained through the CP. Besides taking the hurdle of the pre-submission tradename review process performed by the EMEA via the Invented Name Review Group<sup>59</sup>, it will become even more difficult to find and register acceptable tradenames in the Europe Union, now combining 25 MSs. The CP allows a co-promotional agreement presuming that tradename and packaging layout remain the same consequently any national deviations e.g. such as the local distributor need to be located in the so-called “Blue-Box”, whereas a co-marketing agreement only will be accepted for justified circumstances.

For the MRP/DCP the applicant is able to choose the agency to work with. This condition is still not available in the CP as the Rapporteur and Co-rapporteur are finally chosen by the CHMP. As the final decision of the CHMP could differ from the proposal made by the applicant it is difficult to enter into an effective dialogue with the Rapporteur well in advance of the filing. The early selection process of the MSs for the MRP/DCP is one of the great advantages.

Important selection criteria for the RMS are its flexibility and cooperation strength in case of divergent opinions, its ability to anticipate the comments/concerns from the MSs involved their presence in international parties, e.g. EMEA working parties or ICH. The most important aspect is its ability to defend its original position as RMS. The RMS should be selected very carefully, taking into account its major role as co-ordinator during the procedure. Furthermore, it needs to be evaluated if the agency is able to provide the necessary expertise in the specific therapeutic area and how is their relationship to other agencies. To make the review of a marketing authorisation application as effective as possible, the European Competent Authorities have been asked by the European Commission to specify their scientific expertise, to form so-called “Centres of Excellence” differentiating between specialists and full provider.

Prior to the selection of the CMSs to be involved it needs to be assessed if there are national requirements, guidelines and common medicinal practice that could be a potential risk for a positive outcome and therefore increase the risk for discussion at the CG or finally at the CHMP (arbitration). The applicant should evaluate if there are any concerns known from the assessment of



similar medicinal products and if there are Opinion Leaders known to get involved in the scientific discussion if useful and necessary.

The first contact with a potential RMS/CMS could be initiated through a scientific advice meeting. It provides the chance of the applicant to introduce the product, to clarify any formal pre-submission questions (timelines, documentation), to be aware of the agency's experts involved in the assessment, to evaluate any issues for discussion and to establish an open and close relationship with the agency. The latter aspects also apply to the selection of the Rapporteur/Co-rapporteur.

For products under development which require considerable scientific feedback from various MSs, the CP may be the procedure of choice offering scientific advice on a regular basis provided by the CHMP. In particular for products for which no therapeutic European guidelines are available, the CP may be the better alternative to achieve a unique EU-wide pre-submission assessment.

The CP is characterised by a lack of transparency whereas in the MRP/DCP all MSs' positions on the application are known and shared with the applicant.

In addition the local support of the subsidiary should be a criterion as well as their possibilities to communicate with the local agency. For all procedures it is preferable to have local subsidiaries to handle submissions and clarify regulatory issues (e.g. timelines, documentation, open questions etc.) and built up a close collaboration ship with the agency. Short communication lines should allow a more effective completion of the MA procedure. Considering the project management of the procedures, the CP can be co-ordinated through a single European office whereas the MRP/DCP requires more locally presented resources.

Theoretically the revised CP should allow a quicker market entry than the MRP/DCP, however taking into account the extension of the scope of the CP which may lead to an "overload", future statistics summarising the timelines in practice need to be awaited. However, a major benefit of the CP is the provision of measures to achieve a fast market entry of the product, i.e. the accelerated approval, MA under exceptional circumstances and conditional approval.

Differences remain with respect to the final vote for approval/non-approval. In the MRP/DCP agreement between all MSs involved needs to be reached, except for those countries where the product has been withdrawn before the European step, whereas the MA is centrally approved by a CHMP majority vote. As described in Chapter 5.1.1, in general it is possible to withdraw a MA application in one or more MSs, whereas the CP requires withdrawal in all MSs.

Finally each company needs to develop its own strategy based on the nature of the product, its European organisation structure and its experience to date.

Table 2: Criteria for Selection of the appropriate Marketing Authorisation (MA) Procedure

Criteria	MRP/DCP	CP
<b>Scope</b>	<ul style="list-style-type: none"> <li>– New active substances</li> <li>– Fixed combination products of known substances (those not mandatory for CP)</li> <li>– Generics</li> <li>– OTC products</li> <li>– Blood products</li> <li>– Immunologicals</li> <li>– Traditional herbal medicinal products</li> </ul>	<p>Mandatory:</p> <ul style="list-style-type: none"> <li>– Biotech products incl. generics</li> <li>– New active substances (HIV, diabetes, cancer neurodegenerative disorder) orphan drugs</li> </ul> <p>Optional:</p> <ul style="list-style-type: none"> <li>– Any other new active substances Significant innovations of known substances (article 3)</li> <li>– Generics of centrally authorised products (except biotech products)</li> <li>– Products in the interests of patients at Community level</li> </ul>
<b>Market</b>	Free choice of EU countries to be involved	All EU Member States involved
<b>Duration</b>	~ 480 d/~420 d (incl. clock-stop & CG)	~ 367 d (incl. clock-stop & CD)
<b>Fast review/ Fast MA</b>	MRP: Possible in the national step (1 <sup>st</sup> MA by RMS)	<ul style="list-style-type: none"> <li>– Accelerated procedure (150 d to CHMP Opinion)</li> <li>– Exceptional circumstances</li> <li>– Conditional approval</li> </ul>
<b>Tradename</b>	Different tradenames possible	Only one tradename (article 6); exceptions possible
<b>Co-Promotion</b>	Higher flexibility	Possible („Local Representative“ in Blue Box)
<b>Co-Marketing</b>	Higher flexibility	Not possible; exceptions to be agreed by the Commission
<b>Indication</b>	Higher flexibility as some indications (e.g. hypotension) are not accepted in all MSs	Via majority agreement acceptance in all MSs can be achieved
<b>Agency Expertise (SA)</b>	Free choice of MSs for Scientific Advice	Scientific Advice (via SAWG) of CHMP (EU unique position obtained)
<b>Co-ordinator/ Assessor</b>	Free choice of RMS/CMSSs	Proposal for Rapporteur/ Co-rapporteur; final selection via CHMP
<b>Agreement</b>	Agreement to be reached	CHMP majority vote
<b>Transparency</b>	Easier access to position of individual MSs	Individual position not available
<b>Maintenance/ Project Management</b>	Higher workload due to national MAs	Less workload due to centralised management
<b>Withdrawal</b>	In general possible in one or more MSs	To be done in all MSs
<b>Pack Sizes/ Samples</b>	Higher flexibility	-
<b>Clones</b>	Possible	Not possible; one MA only; exceptions to be agreed by the Commission
<b>Costs</b>	-	Lower compared to the total sum of national fees; reduced costs for SMEs

## 8 Conclusion and Outlook

Generally it could be concluded that the NML provides - at least in theory - in most aspects a “win-win situation” for all parties involved. It is in everyone’s interest that new medicinal products are put on the market more quickly as intended to achieve via reduced marketing authorisation timelines and simplified and efficacious assessment processes. However, currently the advantages can only be identified on a theoretical basis, whether the NML really fulfils what is expected still needs to be seen in practice.

It needs to be ensured that all parties involved fulfil their new obligations to ensure a high level of public health.

The pharmaceutical industry generally welcomes the provisions of the NML. The retaining of the current marketing authorisation systems and the addition of the DCP together with the new scope of the CP provide a great flexibility of choice between the different systems for marketing authorisation. The national marketing authorisation procedures, MRP/DCP, still allow the national agencies to maintain their role in new medicines evaluation. In contrast, as the CP has been strengthened and will become more important in the future, the influence and contribution of national agencies with respect to new marketing authorisations will more and more decrease. The pharmaceutical industry strongly postulates that the national authorities continue to be involved in the new Community system, even though maintaining a major decentralised evaluation capability.

Regarding intellectual property rights it could be predicted that the issue of data protection will continue to be a source of litigation requiring further clarification and interpretation from the courts.

There are still challenges to be addressed in terms of ways of working together. The year 2005 will be a big challenge for the EMEA to fulfil their key objectives, i.e. the implementation of the NML, the optimisation of EMEA’s core business and the implementation of EU Telematics as stated in the EMEA Work Program 2005 and the EMEA Road Map to 2010<sup>60,61</sup>. The set up of a CHMP/EMEA Pharmaceutical Legislation Implementation Task Force was one of the main topics addressed during the January 2005 CHMP Plenary Meeting<sup>62</sup>. This task force will meet on a monthly basis to discuss and review the progress made with the establishment of guidance to enable the implementation of Regulation 726/2004/EC.

For the near future the pharmaceutical industry would highly appreciate if all marketing authorisation procedures should apply the same criteria for evaluation of a marketing application as well as for the assessment of the product throughout the whole lifecycle. Further progress into this direction remains to be seen.

The new rules provide that at least every ten years, i.e. no later than 2014, the EU commission must publish a report on the experience acquired based on the revised authorisation procedures, and propose any amendments for

improvement. This report must be submitted to the European Parliament and the Council. By the time this subject is being reconsidered it is expected that the EMEA will be in a stronger position to demonstrate that it will be able to handle a large amount of applications as a result of making the CP mandatory for all new medicinal products<sup>63</sup>.

## 9 Summary

The current pharmaceutical legislation obliged the European Commission (EC) to report on the experience acquired as a result of the operation of the two marketing authorisation procedures within six years of the entry into force of the Regulation 2309/93/EC. Directive 2004/27/EC amending Directive 2001/83/EC and Regulation 726/2004/EC contain the final provisions of the Review of the pharmaceutical legislation with respect to medicinal products for human use. Necessary legislative amendments include changes to the marketing authorisation procedures, as well as to other aspects such as restructuring of the EMEA, data protection, labelling, validity on marketing authorisation (MA), pharmacovigilance, generic applications and Good Manufacturing Practice.

The major benefit of the changes goes in line with the major objectives of the “Review 2001”, namely to ensure a high level of public health protection for European Union (EU) citizens, to strengthen the European Single Market, to increase competitiveness and transparency and finally to be prepared for the EU enlargement.

The centralised procedure (CP) leads to a single marketing authorisation valid throughout the whole Community. It is granted in the form of a Commission Decision, which is based on a scientific evaluation by the committees created within the European Medicines Agency (EMA). This procedure is now mandatory for biotechnology products (including generics), products for the treatment of AIDS, cancer, neurodegenerative disorders or diabetes, as well as designated orphan medicinal products.

The decision-making process has been improved to allow a faster conclusion of the post-evaluation phase. In particular to ensure a rapid access to innovative products a fast track procedure has been established within the CP. Further changes affecting the CP allow a conditional authorisation for treatments intended for life-threatening, chronic or debilitating conditions. In addition a framework to allow prescription on a compassionate use basis will be put in place.

For those medicinal products, not eligible for the centralised procedure or where the applicant chooses not to follow the centralised procedure, the NML provides a mutual recognition procedure (MRP) for products where a MA already has been granted in one or more Member States and a decentralised procedure (DCP) for products that have not been authorised in any MS before. If during the 90-day European phase no agreement could be reached, the matter of concern will be referred to the Co-ordination Group (CG; legalisation of the former MRFG). Within the CG discussion all the Member States concerned by the application shall use their best endeavours to come to an overall agreement on the issue. If they fail, the matter is referred to the EMA where an arbitration (referral) procedure is followed. New for both procedures is that besides the SmPC, the Patient Information Leaflet as well as the primary and secondary labelling is part of the approval thus providing a harmonised labelling throughout the EU comparable to the CP. The DCP provides a consultation between all Member States involved before the first MA is issued and in contrast to the MRP introduces a clock-stop period within

the first assessment phase mainly conducted by the RMS. In addition through the DCP the MA is obtained at the same time in all Member States involved.

In general the pharmaceutical research industry welcomes the provisions of the NML. However, the promised overall benefit needs to be proven in practice. Several concerns remain amongst others with respect to transparency of the CP, the decreasing involvement of the national Competent Authorities (CA), the ability of the national CA to comply with the timelines currently proposed for the MRP and DCP and the ability of the CA to initiate additional pharmacovigilance evaluations at any time. Further clarification is required with regard to the national implementation of the new legislation in particular for the provisions concerning labelling, data protection, renewal and “Sunset Clause”.

Many criteria need to be carefully considered by the applicant to define the most appropriate MA strategy except in those cases where the procedure is already predefined by the classification of the medicinal product. Advantages of the MRP/DCP include its high flexibility with regard to market selection, co-promotion/co-marketing activities, trademarks, and samples. Time to market for the first MA granted by the RMS (MRP only) as well as the transparency of the assessment process is an additional benefit. The CP is less flexible than the MRP/DCP in terms of trademarks, co-promotion/co-marketing and duplicate applications. However, a major benefit of the CP is the provision of new measures to achieve a fast market entry of the product.

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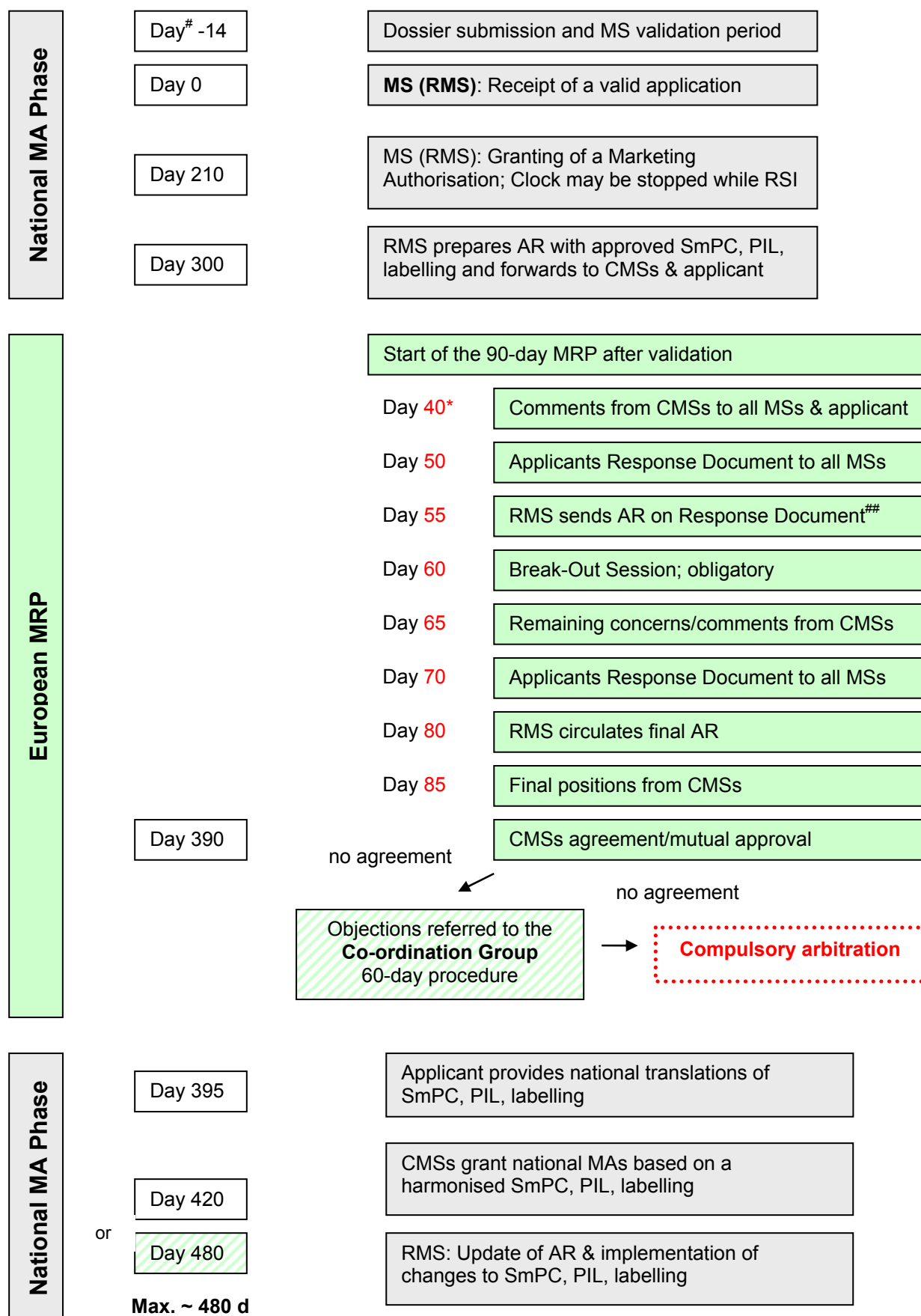
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- <sup>50</sup> EFPIA Comments on Recommendations Concerning the Braille Requirements for Labelling and the Package Leaflet (Article 56a, Directive 2004/27). 23 February 2005. *Draft version, not finalised yet*



- <sup>51</sup> VFA comments on the draft EU-Commission “Recommendation concerning the Braille requirements for labeling and the package leaflet (art. 56a, Dir. 2004/27)”. 8 February 2005.
- <sup>52</sup> Vorläufige Stellungnahme des Bundesverbandes der Pharmazeutischen Industrie e.V. zum Referentenentwurf für ein Vierzehntes Gesetz zur Änderung des Arzneimittelgesetzes. 28. Februar 2005
- <sup>53</sup> Bundesministerium für Gesundheit und Soziale Sicherung (BMGS): Gesetz über den Verkehr mit Arzneimitteln („Kleine AMG-Novelle“). Veröffentlichung im Bundesgesetzblatt am 26. April 2005
- <sup>54</sup> Kleine AMG-Novelle im Bundesrat unverändert verabschiedet. VFA Infobrief Nr. 12/2005. 18 März 2005
- <sup>55</sup> Notice to Applicants Volume 9: Pharmacovigilance. June 2004
- <sup>56</sup> EFPIA Comments on FML Implementation of Renewals and the Sunset Clause. July 2004. *Draft version, not finalised yet*
- <sup>57</sup> Anhörung zur 14. AMG-Novelle – VFA bringt seine Positionen ein. VFA Infobrief Nr. 9/2005. 2. März 2005
- <sup>58</sup> Löfgren M., Dreesen M., New Drug Approval in the European Union, Parexel International Corporation, Waltham, MA, 2002
- <sup>59</sup> Guideline on the Acceptability of Invented Names for Human Medicinal Products Processed through the Centralised Procedure. CPMP/328/98 Revision 4, London 14 September 2004
- <sup>60</sup> Work Programme for the European Medicines Agency 2005. EMEA/MB/138351/2004/en/Final. Adopted by the Management Board on 16 December 2004
- <sup>61</sup> The European Medicines Agency Road Map to 2010: Preparing the Ground for the Future. EMEA/H/34163/03/Final, 4 March 2005
- <sup>62</sup> Committee For Medicinal Products For Human Use. January 2005 Plenary Meeting Monthly Report. EMEA/22735/2005 corr. 1 February 2005
- <sup>63</sup> Pickup Z., Does the New EU Medicines Law strengthen Industry while Improving the Public Health? Regulatory Affairs Journal Pharma, May 2004, p. 323-328

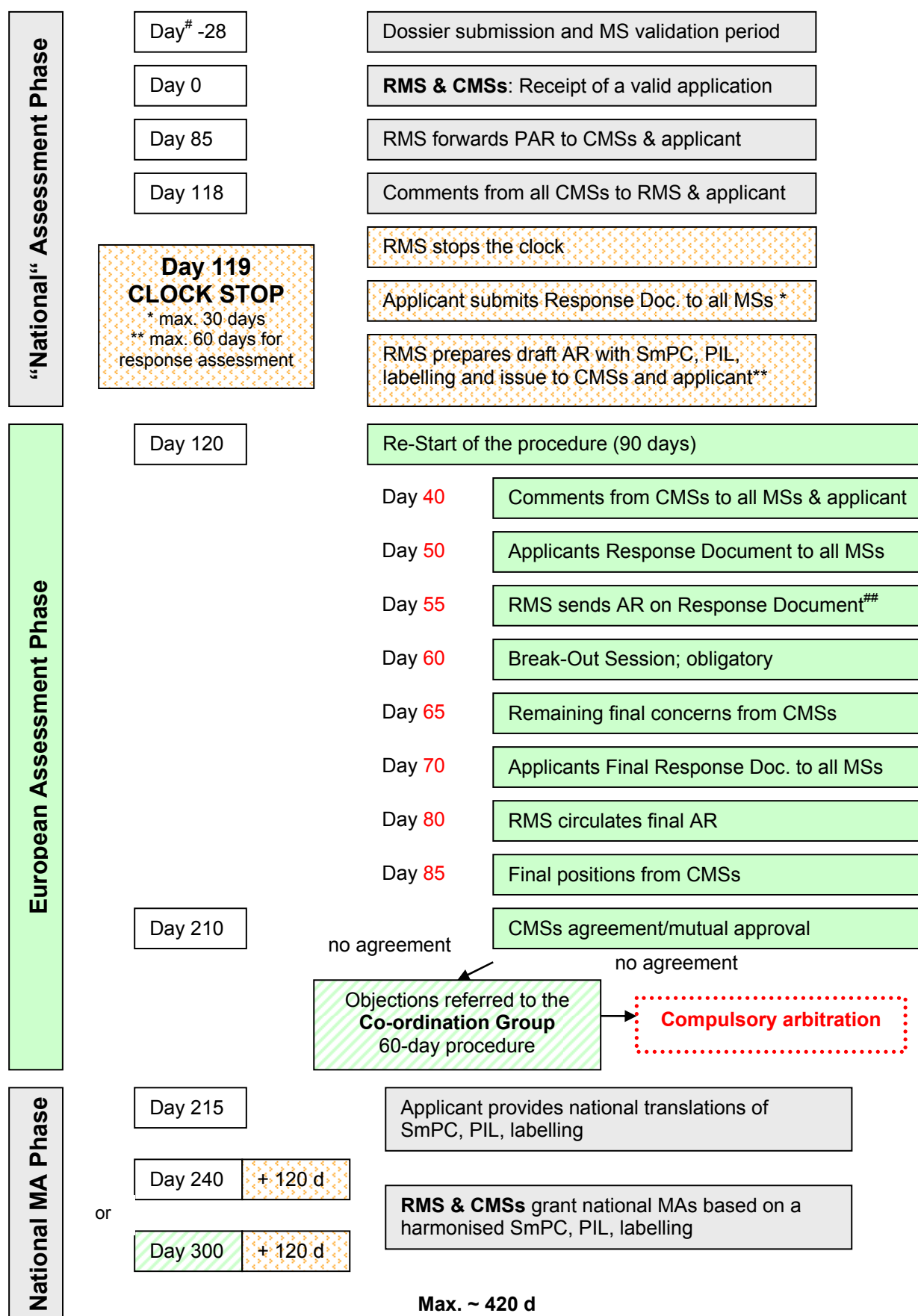
## **Annexes**

## Annex I: The “New” Mutual Recognition Procedure



\* current draft proposal for timelines; # calendar days

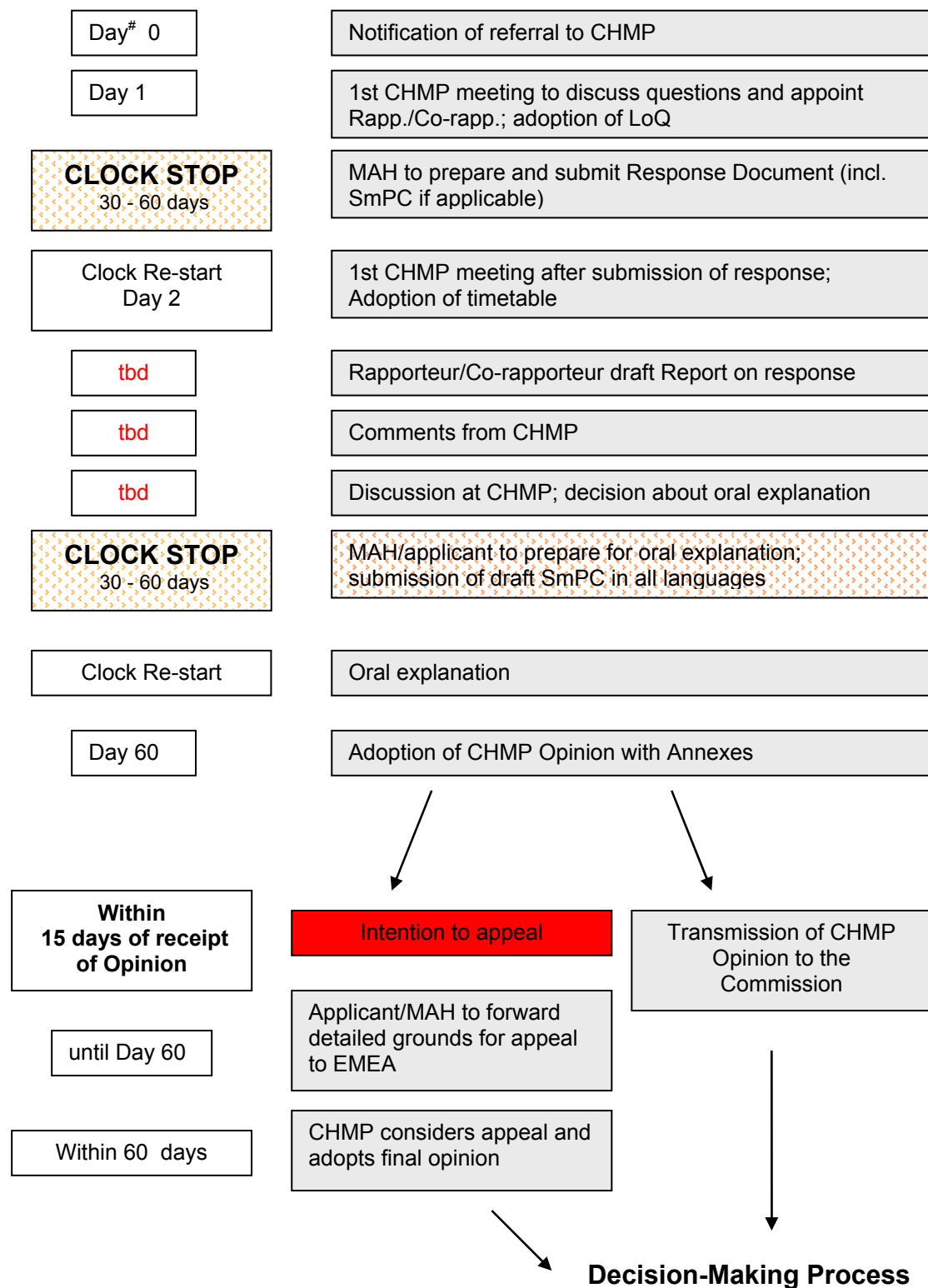
<sup>##</sup> Day 56-59 : CMSs provide outstanding issues and need for Break-Out Session

**Annex II: The Decentralised Procedure (Final Draft)<sup>§</sup>**

<sup>§</sup> Adopted as internal working document of the MRFG on 18 October 2004; <sup>#</sup> calendar days

<sup>##</sup> Day 56-59 : CMSs provide outstanding issues and need for Break-Out Session

### Annex III: Referral (Arbitration) & Appeal

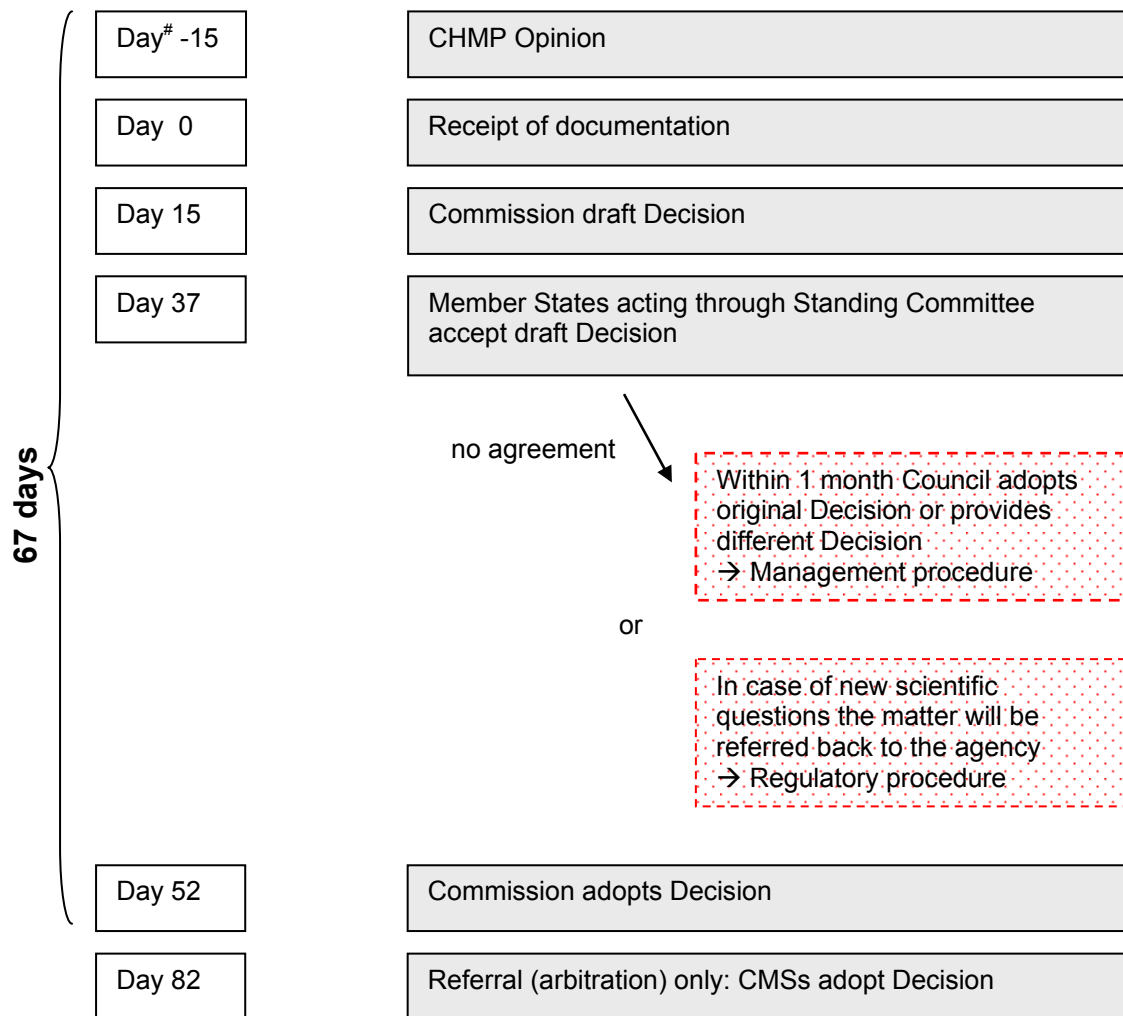


**Annex IV: The Centralised Procedure**

<b>Preliminary Assessment</b>	Day <sup>#</sup> -14	Dossier submission and EMEA validation period
	Day 0	Start of the procedure
	<b>Day 80</b>	Rapporteur/Co-rapporteur forwards PAR to applicant, CHMP and EMEA
	Day 100	Comments from CHMP
	Day 115	Rapporteur/Co-rapporteur forwards draft LoQ to CHMP and EMEA
	<b>Day 120 CLOCK STOP</b> 30 - 60 days	CHMP adopts LoQ to be sent to the applicant
<b>Opinion Making Process</b>	Day 121	Restart: Applicant submits Response Document
	Day 150	Rapporteur/Co-rapporteur forwards Common Response AR to CHMP, EMEA and applicant
	Day 170	Comments from CHMP
	Day 180	CHMP discussion about the need for an oral explanation
	<b>CLOCK STOP in case of oral explanation ~ 30 days</b>	
	Day 181	Restart and oral explanation
	Day 185	Final draft of SmPC, PIL and labelling to be forwarded to Rapp/Co-Rapp., CHMP and EMEA
	Day 210	Adoption of CHMP Opinion and AR
<b>Preparation for CD</b>	tbd	Final SmPC, PIL and labelling in all languages to be forwarded to CHMP and EMEA
	tbd	After linguistic comments, revised final SmPC, PIL and labelling in all languages to be forwarded to CHMP and EMEA
	tbd	Final SmPC, PIL and labelling in all languages and color mock-ups to be forwarded to CHMP and EMEA
	Day 225	Final CHMP AR and Opinion in all languages to be forwarded to Commission, MSs & applicant
	Day 277	Commission Decision
	<b>Max. ~ 367 d</b>	

<sup>#</sup> calendar days

## Annex V: Decision-Making Process following CP-CHMP Opinion, Referral or MRP/DCP Arbitration



<sup>#</sup> calendar days

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München, den \_\_\_\_\_