The Global Marketing Authorisation

according to Article 6 of Directive 2001/83/EC, as amended

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List of Abbreviations

CMD(h)	Co-ordination Group of Mutual Recognition and Decentralised Procedures – Human
ECJ	European Court of Justice
EU	European Union
EMEA	European Medicines (Evaluation) Agency
MA	Marketing Authorisation
MCA	Medicines Control Agency former name of the competent authority in the United Kingdom
MHRA	Medicines and Healthcare products Regulatory Agency competent authority in the United Kingdom
NtA	Notice to Applicants
PSUR	Periodic Safety Update Report

1. Introduction

With coming into force of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended a new regulatory concept has been introduced into the European legislation – the **global marketing authorisation** according to Article 6 (1).

1.1 Article 6 (1) of Directive 2001/83/EC, as amended

No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authorities of that Member State in accordance with this Directive or an authorisation has been granted in accordance with Regulation (EEC) No 2309/93.

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same **global marketing authorisation**, in particular for the purpose of the application of Article 10 (1). [1]

1.1.1 Variation – Extension

According to Commission Regulation (EC) No 1084/2003 [2] Article 3 (1)(a) a Variation to the terms of a marketing authorisation for medicinal products for human is defined as an amendment to the contents of the documents referred to in Articles 8 to 12 of Directive 2001/83/EC.

Three different types of variations are defined in order to take the different needs for a change to a marketing authorisation into account.

Minor variations of Type IA or Type IB, listed in Annex I of the Regulation together with the conditions that must be fulfilled and major variations of Type II, which cannot be deemed to be a minor variation or an extension of the marketing authorisation.

To decide whether the change is a Type II variation or an extension of the marketing authorisation a separate NtA Notice to Applicants ′Guideline on the categorisation of

extension application versus variation applications′ [3] has been published by the European Commission.

Extensions of marketing authorisations which fulfil the conditions as set out in Annex II to Regulation (EC) No 1084/2003 are falling outside the definition of a variation to a marketing authorisation according to Article 2 (a) of Regulation 1084/2003. [3]
According to Annex II [2], changes to a marketing authorisation leading to an extension application are for example:

1. Changes to the active substance(s):

(i) replacement of the active substance(s) by a different salt/ester, complex/derivate with the same therapeutic moiety where the efficacy/safety characteristics are not significantly different;
(ii) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer) where the efficacy/safety characteristics are not significantly different.

2. Changes to strength, pharmaceutical form and route of administration:

(i) change of bioavailability;
(ii) change of pharmacokinetics e.g. change in rate of release;
(iii) change or addition of new strength/potency;
(iv) change or addition of a new pharmaceutical form;
(v) change or addition of a new route of administration.

This extensions shall be examined in accordance with the procedure as referred to in Article 17 of Directive 2001/83/EC, which is the same as for granting a new marketing authorisation by the competent authorities.

For the purpose of regulating data protection periods and market exclusivity rights as mentioned in Article 10 (1), the incorporation of the concept of global marketing authorisation according Article 6 (1) into pharmaceutical legislation seems to be obvious.

Especially, when considering Paragraph (9) of Directive 2001/83/EC, as amended where it is stated that ′Experience has shown that it is advisable to stipulate more precisely the cases in which the results of toxicological and pharmacological tests or clinical trials do not have to be provided with a view to obtaining authorisation for a medicinal product which is essentially similar to an authorised product, while ensuring that innovative firms are not placed at a disadvantage.′ [1]

Nevertheless, this new regulatory concept of a global marketing authorisation implicates basis for discussion. It has to be seen in context with all other regulatory requirements being relevant for a marketing authorisation as defined before coming into force of Article 6 of Directive 2001/83/EC, as amended and not restricted to Article 10 (1).

In the following the new concept of global marketing authorisation according Article 6 (1) of Directive 2001/83/EC, as amended, shall be examined from two different perspectives.

1. On the one hand with regard to the legislation previous to Directive 2001/83/EC, as amended and several judgements from the European Court of Justice based on that legal basis. These judgements led to the current wording of Article 6 (1) and Article 10 and introducing them into pharmaceutical legislation.

2. On the other hand with regard to the impact on miscellaneous Articles within the current regulatory environment as laid down in Directive 2001/83/EC, as amended.

2. Legislation previous to Directive 2001/83/EC, as amended – ECJ-Judgements

With adopting Directive 2001/83/EC on the Community code relating to medicinal products and including the concept of the global marketing authorisation into Article 6 and adopting Article 10 (1), 10 (2) and 10 (3) within the European legislation the European Parliament and the Council followed several decisions from the European Court of Justice, ECJ, that had been issued.

The ECJ based its decisions on the legislation into force at the time of the ruling, previous to the current version of Directive 2001/83/EC, as amended.

2.1 Legislation previous to Directive 2001/83/EC, as amended

2.1.1 Directive 65/65/EEC as amended by Directive 87/21/EEC

This Directive 65/65/EEC [4] as legal basis is relevant for the Generics Case – C-368/96, the Novartis Case – C-106/01 and the SmithKline Beecham Case – C-74/03.

2.1.1.1 Article 3

No proprietary medicinal product may be placed on the market in a Member State unless an authorisation has been issued by the competent authority of that Member State.

2.1.1.2 Article 4

In order to obtain an authorisation to place a proprietary medicinal product on the market as provided for in Article 3, the person responsible for placing that product on the market shall make application to the competent authority of the Member State concerned.

The application shall be accompanied by the following particulars and documents:

(8) Results of: physico-chemical, biological or microbiological tests – pharmacological and toxicological tests – clinical trials.

However, and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:

(i) either that the medicinal product is essentially similar to a product authorised in the country concerned by the application and that the person responsible for the marketing of the original medicinal product has consented to the pharmacological, toxicological or clinical references contained in the file on the original medicinal product being used for the purpose of examining the application in question;

(ii) or by detailed references to published scientific literature presented in accordance with the second paragraph of Article 1 of Directive 75/318/EEC that the constituent or constituents of the medicinal product have a well established medicinal use, with recognised efficacy and an acceptable level of safety;

(iii) or that the medicinal product is essentially similar to a product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made; this period shall be extended to 10 years in the case of high-technology medicinal products within the meaning of Part A in the Annex to Directive 87/22/EEC or of a medicinal product within the meaning of Part B in the Annex to that Directive for which the procedure laid down in Article 2 thereof has been followed; furthermore, a Member State may also extend this period to 10

years by a single Decision covering all the products marketed on its territory where it considers this necessary in the interest of public health. Member States are at liberty not to apply the abovementioned six-year period beyond the date of expiry of a patent protecting the original product.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate pharmacological and toxicological texts and/or of appropriate clinical trials must be provided. [4]

The procedures established by Article 4.8 (a)(i), (ii) and (iii) of Directive 65/65/EEC, as amended, are commonly known as ′abridged procedures′. The specific procedure for obtaining marketing authorisation laid down by the last subparagraph of Article 4.8 (a) – the proviso – is known as the ′hybrid′ abridged procedure.

It enables a second applicant for marketing authorisation for a given product to save the time and expense necessary in order to gather the pharmacological, toxicological and clinical data. In accordance with the fourth recital in the preamble to Directive 87/21/EEC, it also avoids, on public policy grounds, the repetition of tests on humans or animals where not absolutely necessary.

2.1.1.3 Article 5

The authorisation provided for in Article 3 shall be refused if, after verification of the particulars and documents listed in Article 4, it proves that the proprietary medicinal product is harmful in the normal conditions of use, or that its therapeutic efficacy is lacking or is insufficiently substantiated by the applicant, or that its qualitative and quantitative composition is not as declared. [4]

2.1.2 Directive 2001/83/EC before coming into force of Directive 2004/27/EC amending Directive 2001/83/EC

This Directive as legal basis is relevant for the Eli Lilly Case – C-36/03.

2.1.2.1 Article 6 (1)

No medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued.

2.1.2.2 Article 8 (3)

The application – for the grant of a marketing authorisation – shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(i) Results of physico-chemical, biological or microbiological tests – toxicological and pharmacological tests – clinical trials.

2.1.2.3 Article 10 (1)(a)

In the version in force before Directive 2004/27/EC amending Directive 2001/83/EC came into force, Article 10 (1)(a) of Directive 2001/83/EC provided:

In derogation of Article 8 (3)(i), and without prejudice to the law relating to the protection of industrial and commercial property:

(a) The applicant shall not be required to provide the results of toxicological and pharmacological tests or the results of clinical trials if he can demonstrate:

(iii) that the medicinal product is essentially similar to a medicinal product which has been authorised within the Community, in accordance with Community provisions in force, for not less than six years and is marketed in the Member State for which the application is made. This period shall be extended to 10 years in the case of high-technology medicinal products having been authorized according to the procedure laid down in Article 2 (5) of Council Directive 87/22/EEC. Furthermore, a Member State may also extend this period to 10 years by a single decision covering all the medicinal products marketed on its territory where it considers this necessary in the interest of public health. Member states are at liberty not to apply the six-year period beyond the date of expiry of a patent protecting the original medicinal product.

However, where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses, the results of appropriate toxicological and pharmacological tests and/or of appropriate clinical trials must be provided.′ [5]

The procedures laid down in Article 10 (1)(a)(i) to (iii) of Directive 2001/83/EC are commonly known as ′abridged procedures′. The special procedure for obtaining marketing authorisation provided for in the final paragraph of Article 10 (1)(a) – ′the proviso′ – is known as a ′hybrid′ abridged procedure.

2.1.3 Regulation (EC) No 541/95 – Annex II

This Directive as legal basis is relevant for the Generics Case – C-368/96 and the SmithKline Beecham Case – C-74/03.

Annex II to Commission Regulation (EC) No 541/95 of 10 March 1995 concerning the examination of variations to the terms of a marketing authorisation granted by a competent authority of a Member State [6] provides that certain changes to a marketing authorisation, a list of which is set out in that Annex, are to be considered to fundamentally alter the terms of that authorisation and therefore to require an application for a new marketing authorisation to be made, and not merely an application to vary the terms of the marketing authorisation. Amongst the changes which require a new application are, inter alia, the addition of an indication in a different therapeutic area, the addition of a new strength and the addition of a new route of administration.

The following four judgements relating to aspects such as essential similarity, data protection, or the abridged application procedure for medicinal products had significant influence leading to the current wording of Articles 6, 10 (1), 10 (2) and 10 (3) of Directive 2001/83/EC, as amended, and a common understanding of the above mentioned regulatory aspects.

2.2 Judgement of the Court from 3 December 1998

Generics Case – C-368/96 [7]

This judgement is about the interpretation and validity of Article 4.8 (a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating, to medicinal products.

2.2.1 The dispute in the main proceedings

There are three sets of proceedings summarised in Case C-368/96 known as the Generics Case.

1. Bristol-Myers Squibb Pharmaceuticals Limited obtained the first marketing authorisation for Captopril in Germany in 1981. In the same year E.R. Squibb & Sons Limited a subsidiary of Bristol-Myers Squibb Pharmaceuticals Limited, obtained a

marketing authorisation for Captopril in the United Kingdom for new therapeutic indications.

In 1993 Generics, as a manufacturer and distributor of generic medicinal products, submitted to the Medicines Control Agency of the United Kingdom, MCA, under the provision at issue, an abridged application for a marketing authorisation for Captopril. The MCA granted marketing authorisations for Captopril in respect of indications which had been authorised in any Member State of the European Union for not less than 10 years but refused to grant it marketing authorisations for any indications which had not been approved for at least 10 years.

The MCA stated that a second applicant could refer to original data pursuant to Article 4.8 (a)(iii) of Directive 65/65/EC as amended, for changes which did not satisfy the criteria laid down in Annex II to Regulation No 541/95. This means that for indications added during the preceding 10 years, and requiring a new application under Annex II to Regulation No 541/95, either subject of a new application or incorporated into the original marketing authorisation, a protection of new data submitted in support of the change would be given for a period of 10 years.

2. Wellcome was granted marketing authorisations for Aciclovir in the United Kingdom between 1981 and 1994, including several new indications, dosage forms and routes of administration. In 1996 A/S Gea Farmaceutisk Fabrik obtained marketing authorisations for all the therapeutic indications and dosage forms of Aciclovir tablets and intravenous infusion for which Wellcome had obtained authorisations in the United Kingdom at that date.

Wellcome lodged an application for judicial review of the MCA's decision to grant A/S Gea Farmaceutisk Fabrik marketing authorisations under the abridged procedure in respect of therapeutic indications, routes of administration and dosage forms for Aciclovir tablets and intravenous infusion which had been approved in the Community for less than 10 years.

3. Glaxo obtained all marketing authorisations for Ranitidine granted in the United Kingdom between 1981 and 1995. Following the submission by Generics of an abridged application for marketing authorisation in respect of Ranitidine tablets, the MCA stated that it considered, that subsequent applications for marketing authorisations for products containing Ranitidine could rely on the provision at issue for all the indications, doses and dosage schedules authorised for the originator – not taking into account the right to protection of these additional data.

Glaxo applied to the national Court for judicial review of the MCA's decision in respect of indications, doses and dosage schedules for Ranitidine tablets which had been the subject of marketing authorisations granted less than 10 years previously.

The innovative pharmaceutical companies, Bristol-Myers Squibb Pharmaceuticals Limited, Wellcome and Glaxo agree that the abridged procedure in question only applies if the applicant shows that the composition of the product for which it has applied for a marketing authorisation is comparable to the original product, which must have been authorised for not less than 10 years. The same applies for each therapeutic indication, dose, dosage form or dosage schedule for which the marketing authorisation is applied for by a generic company.

In contradiction hereto the generic companies argue that under the abridged procedure a marketing authorisation may be granted for any indication, dose, dosage form or dosage schedule for which the original product was authorised, irrespective of when the marketing authorisation was varied or the new marketing authorisation was granted. It has to be shown that the composition of the product, for which marketing authorisation is requested, is essentially similar to that of an original product which has been authorised for not less than 10 years.

According to the MCA, marketing authorisations may be granted under the abridged procedure, showing essential similarity with regard to the composition, for both the original therapeutic indication, dose, dosage form or dosage schedule and any addition or change to the therapeutic indication, dose, dosage form or dosage schedule for which the original product was authorised, whether or not they have been granted during the last 10 years. The decision depends on whether the new indication satisfies the criteria required under Annex II to Regulation No 541/95 or not, which means whether the new indication, dosage schedule or dosage form can be defined as major therapeutic innovation or not.

2.2.2 Questions referred to the ECJ for a preliminary ruling

The following questions referred to the Court of Justice with relevance for the actual wording of Article 6 (1) and 10 (1) are:

1. What is meant by ′essentially similar′ for the purposes of Article 4.8 (a)(iii) of Council Directive 65/65/EEC, as amended?

2. May Product B be authorised in accordance with Article 4.8 (a)(iii) of Directive 65/65/EEC, as amended, in respect of only those indications for which product A has been authorised in the EU for 6 or 10 years or all indications for which

product A is currently authorised in the relevant Member State at the date of application?

Should there be a differentiation for indications authorised for a shorter period than 6 or 10 years taking into consideration the provisions of Annex II of Regulation 541/95? Means that only these indications may be authorised for Product B which did not require a new application respectively if the indication in question was added by variation to an existing authorisation for Product A.

3. May product B be authorised in accordance with Article 4.8 (a)(iii) of Directive 65/65/EEC as amended in respect of only those dosage forms and/or doses and/or dosage schedules for which product A has been authorised in the EU in accordance with Community provisions in force for 6 or 10 years or all dosage forms and/or doses and/or dosage schedules for which product A is currently authorised in the relevant Member State at the date of the application made in relation to product B?

   Should there be a differentiation for indications authorised for a shorter period than 6 or 10 years taking into consideration the provisions of Annex II of Regulation 541/95?

2.2.2.1 The first question

The abridged procedure frees the applicant from the obligation to carry out the pharmacological and toxicological tests and clinical trials referred to in Article 4.8 of Directive 65/65/EEC, the objective of which is to prove the safety and efficacy of medicinal products. It is intended to reduce the time needed to prepare an application for authorisation and to avoid ethically and scientifically inappropriate repetition of these tests.

This does not mean that the requirements of safety and efficacy must not be met by medicinal products authorised under the abridged procedure. The primary purpose of any rule concerning production and distribution of medicinal products must be to safeguard public health as stated in the preamble to Directive 65/65/EEC.

For medicinal products authorised under the provisions of Article 4.8 (a)(iii) the obligation to carry out those tests is replaced by the obligation to show essential similarity to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made.

According to minutes from a meeting of the Council when adopting Directive 87/21/EEC the criteria determining the concept of essential similarity between

medicinal products are that they have the same qualitative and quantitative composition in terms of active principles, the same pharmaceutical form, and, where necessary, bioequivalence of the two products has been established by appropriate bioavailability studies.

Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, is therefore to be interpreted as meaning that a medicinal product is essentially similar to an original medicinal product, where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

2.2.2.2 The second question

Provided that a medicinal product is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made, the applicant is not required, under the provision at issue, to provide the results of pharmacological and toxicological tests or of clinical trials.

The competent authority then uses the pharmacological, toxicological and clinical documentation relating to the original medicinal product for assessment. This documentation covers both the therapeutic indications which have been authorised for not less than 6 or 10 years in the Community and more recent therapeutic indications.

It must therefore be asked whether this documentation concerning indications that have been authorised for less than 6 or 10 years, or at least some of them, enjoy a period of independent protection.

Since having the same therapeutic indications is not one of the criteria which must be satisfied in order that two medicinal products may be regarded as essentially similar it follows that an applicant seeking for marketing authorisation for a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community is not required, under the provision at issue, to supply pharmacological, toxicological and clinical documentation, whatever be the therapeutic indications to which the documentation for the original medicinal product relates.

Consequently, under the abridged procedure provided for in Article 4.8 (a)(iii) of Directive 65/65/EEC, as amended, the applicant may receive marketing authorisation

for all therapeutic indications covered by the documentation of the original medicinal product, including those indications authorised for less than 6 or 10 years.

The argument from the Commission of ensuring fair protection for innovation as the general purpose of the provision at issue by giving independent protection periods for the results of new pharmacological and toxicological tests and clinical trials in exceptional circumstances, e.g. a new indication, is in contrary to the wording of the provision itself, when interpreted in the light of the definition of ′essentially similarity′.

A differentiation for indications authorised for a shorter period than 6 or 10 years taking into consideration the provisions of Annex II of Regulation No 541/95 following the argumentation from MCA cannot be made. On the one hand because of the definition of essential similarity and on the other hand due to the fact, that Annex II states that it is without prejudice to the provisions of Article 4 of Directive 65/65/EEC and that this regulation does no more than harmonise administrative practices.

A medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years and is marketed in the Member State for which the application is made may therefore be authorised, under the abridged procedure provided for in Article 4.8 (a)(iii) of Directive 65/65/EEC, as amended, for all therapeutic indications already authorised for that product.

2.2.2.3 The third question

Assuming that the terms dosage form, dose and dosage schedule as used by the national court do not preclude essential similarity between the medicinal products in accordance with the definition of essential similarity adopted in this judgment, the third question has to be assessed the same way as the second question.

Consequently, having regard to the arguments set out in the context of the second question and the answer to that question, the answer must be that a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years in the Community and is marketed in the Member State for which the application is made may be authorised under the abridged procedure provided for in Article 4.8 (a)(iii) of Directive 65/65/EEC, as amended, for all dosage forms, doses and dosage schedules already authorised for that product.

2.2.3 Summary

This judgement of the Court from 3 December 1998 – Case C-368/96 [4] gives a first definition of essential similarity with regard to Article 4.8 (a)(iii) of Directive 65/65/EEC.

A medicinal product is essentially similar to an original medicinal product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

Additionally, the judgement states clearly that a medicinal product that is essentially similar to a product which has been authorised for not less than 6 or 10 years and is marketed in the Member States for which the application is made may be authorised, under the abridged procedure provided for in Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, for all therapeutic indications respectively for all dosage forms, doses and dosage schedules already authorised for that product.

Consequently, this means that the authorisation of a new therapeutic indication respectively dosage form, dose and dosage schedule for the original medicinal product does not restart or prolong the data protection period of 6 or 10 years for the original medicinal product.

2.2.4 Relevance for Article 6 (1), 10 (1) and 10 (2) of Directive 2001/83/EC, as amended

Within the judgement itself the European Court of Justice states that there would be no dispute that it is, where appropriate, for the Community legislature to adopt measures to reinforce the rules for the protection of innovating undertakings in the harmonised area with which the present case – ECJ C-368/96 – is concerned.

The topics discussed within these ECJ-Case and fixed in the judgement of the European Court of Justice have been taken into consideration when working out the wording for both Article 6(1), Article 10 (1) and Article 10(2). The relevant sections are highlighted.

2.2.4.1 Article 6 (1) – 2001/83/EC

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths,

pharmaceutical form, administration routes, presentations, **as well as any variations and extensions** shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations **shall be considered as belonging to the same global marketing authorisation**, in particular for the purpose of the application of Article 10 (1). [1]

2.2.4.2 Article 10 (1) – 2001/83/EC

The judgment ruling that there is no not restart or prolongation of the data protection period of 6 or 10 years for an additional indication has been attenuated additionally to that effect that the following highlighted sections have been included into Article 10 (1), last paragraph.

By way of derogation from Article 8 (3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.

A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.

The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for a generic medicinal product is submitted. In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to the authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. [1]

2.2.4.3 Article 10 (2) – 2001/83/EC

(b) **'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.** The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivates of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not to be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate guidelines. [1]

2.3 Judgement of the Court from 29 April 2004

Novartis Case – Case C-106/01 [8]

This judgement is as well about the interpretation of Article 4.8 (a) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products.

2.3.1 The dispute in the main proceedings

The pharmaceutical company Novartis, former Sandoz Pharmaceuticals Ltd., obtained a marketing authorisation for the medicinal product Sandimmun in the European Community in the United Kingdom in 1983. In 1994 Novartis obtained the marketing authorisation for Neoral in Germany and in 1995 in the United Kingdom. Both products contain Ciclosporin and only differ in the pharmaceutical form. Sandimmun forms a macroemulsion whilst Neoral forms a microemulsion with a higher bioavailability then Sandimmun.

The application to the Medicines Control Agency, MCA, was made as a hybrid abridged application under Article 4.8 (a)(i) of Directive 65/65/EEC as amended, cross-referring, with the consent of the person responsible, to the data relating to Sandimmun. Data and patent protection have already expired for Sandimmun at this point of time. However, it also included, under the proviso, data from further studies

and clinical trials, in recognition of the fact that Neoral differed in some respects from the reference product.

In 1999, the MCA granted two marketing authorisations to SangStat in respect of SangCya, which forms a nanodispersion based on a hybrid abridged procedure according Art. 4.8 (a) (iii) of Directive 65/65, as amended. The reference product was Sandimmun, which, unlike Neoral, had been authorised in the Community for more than 10 years.

SangStat submitted data to demonstrate the suprabioavailability of SangCya by comparison with Sandimmun and the essential similarity of those products. Studies showing bioequivalence between SangCya and Neoral sold in the United States were also included with the application.

For the purposes of granting marketing authorisations for SangCya the MCA also relied on data submitted by Novartis in support of its Neoral application.

Novartis applied for judicial review and lodged, after dismissal, an appeal before the Court of Appeal stating that:

(a) the MCA cross-referred unlawfully to the Neoral file – cross-reference issue.
(b) the MCA erred in finding that SangCya was essentially similar to Sandimmun, because it is not bioequivalent – essential similarity issue.

In contradiction hereto the MCA argued that:

(a) it was entitled to cross-refer to all information in its possession in assessing whether a product for which marketing authorisation was sought was safe.
(b) questions of essential similarity were inherently questions of fact, degree and expert opinion for the competent national authorities, which enjoy a margin of discretion in deciding issues such as whether two products have the same pharmaceutical form. In any event, bioequivalence is not always required in order to demonstrate essential similarity.

2.3.2 Questions referred to the ECJ for a preliminary ruling

The Court of Appeal decided to stay the proceedings and referred the following questions to the ECJ:

1. Is a national competent authority ever entitled to cross-refer, without consent, to data submitted in support of a Product B which was authorised within the last 6/10 years when examining a marketing authorisation application for a new

Product C under Article 4.8 (a)(iii) of Directive 65/65/EEC, referencing a Product A authorised for more than 6/10 years?

2. If so, may such cross-reference be made where:
   (a) Product B was authorised under the hybrid abridged procedure, referencing Product A and
   (b) the data to which reference is made consists of clinical trials which the national competent authority indicated would be necessary if the marketing authorisation was to be granted and which were submitted in order to demonstrate that Product B is safe?

3. (a) Does the final subparagraph of Article 4.8 (a) of Directive 65/65/EEC – the proviso – apply only to applications made under Article 4.8 (a)(iii) or to applications made under Article 4.8 (a)(i), too?
   (b) Is essential similarity a prerequisite for the use of the proviso?

4. Can products ever be essentially similar for the purposes of Article 4.8 (a)(i) and (iii) of Directive 65/65/EEC when they are not bioequivalent, and if so in what circumstances?

5. What is the meaning of the term pharmaceutical form, as used by the Court in its judgment in Case C-368/96 – the Generics Case?
   In particular, do two products have the same pharmaceutical form when they are administered to the patient in the form of a solution diluted to a macroemulsion, microemulsion and nanodispersion respectively?

2.3.2.1 The fourth question

In Case C-368/96 – the Generics Case – the Court ruled that a medicinal product cannot be regarded as essentially similar to an original medicinal product if it does not satisfy the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent.

The two abridged procedures according to Article 4.8 (a)(i) respectively Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, differ only in the right to refer to the pharmacological, toxicological or clinical documentation contained in the file of the reference medicinal product. In the first case the consent of the person responsible for the marketing of that medicinal product is necessary, in the second case, the reference medicinal product must have been authorised for not less than 6 or 10 years.

Consequently, for both applications for the purpose of Article 4.8 (a)(i) or (iii) of Directive 65/65/EEC as amended, products cannot be regarded as essentially similar where they are not bioequivalent.

2.3.2.2 The fifth question

The concept of pharmaceutical form is not defined in neither Directive 65/65/EEC as amended, nor in the Community legislation.

According to relevant information, e.g. from the European Pharmacopoeia and others, the form in which the pharmaceutical product is presented by the manufacturer and the form in which it is administered including the pharmaceutical form must be taken into account.

In that context, medicinal products presented in the form of a solution to be mixed in a drink for administration to the patient and which, after mixing, form, respectively a macroemulsion, a microemulsion and a nanodispersion, are to be treated as having the same pharmaceutical form, provided that the differences in the form of administration are not significant in scientific terms.

2.3.2.3 Third question – first part

The proviso, which means the hybrid abridged procedure laid down by the final subparagraph of Article 4.8 (a) of Directive 65/65/EEC as amended, applies to applications for marketing authorisation based on Article 4.8 (a)(i) or (iii). It does not appear that there is a difference between those two abridged procedures – informed consent and generic. If it is ethically and scientifically inappropriate to repeat all tests for an application, which otherwise satisfies all the requirements under Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, it is also inappropriate to repeat those tests for an application which otherwise satisfies the requirements set out in Article 4.8 (a)(i).

2.3.2.4 Third question – second part

According to the wording of Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, read in strict conjunction with the proviso, essential similarity is a prerequisite for applications under the proviso.

In Case C-368/96 – the Generics Case – the Court ruled that a medicinal product cannot be regarded as essentially similar to an original medicinal product if it does not satisfy the criteria of being bioequivalent.

Then the proviso would be largely ineffective as it could never be applied for products which are administered by different routes or in different doses since they are in general not bioequivalent to the reference medicinal product and therefore not essentially similar per definition. The proviso would then be restricted to pharmaceutical products intended for a different therapeutic use only.

Taking into consideration once more a fact of Case C-368/96, the purpose of the applicant's obligation under the proviso is to provide the results of appropriate pharmacological and toxicological tests and clinical trials to prove the safety and efficacy of the medicinal product.

An application may be made under the proviso if the medicinal product for which marketing authorisation is applied for is essentially similar to the reference medicinal product, unless one or more of the differences set out in the proviso, such as different therapeutic use, different route or different dose apply.

2.3.2.5 The first and second questions

According to the judgement in the Generics Case, C-368/96, an applicant for marketing authorisation for a medicinal product essentially similar to a product authorised for at least 6 or 10 years in the Community is not required to supply pharmacological, toxicological and clinical documentation for any of the therapeutic indications to which the documentation for the original medicinal product relates, including those, authorised for less than 6 or 10 years.

With respect to the proviso, the same applies for a medicinal product which is to be administered by routes or in doses different from those of other medicinal products on the market.

It is not decisive in that context that the different products generally satisfy all the criteria for essential similarity. A strict requirement would hinder the cross-referring for different routes or doses.

Therefore, the applicant for marketing authorisation for a medicinal product may refer to that documentation where the products resulting from the ongoing development of the reference medicinal product and the reference medicinal product are essentially similar, apart from the route of administration or the dose, as the case may be.

If Product B resulting from the development of reference Product A is essentially similar to that reference product, apart from its bioavailability, since that difference is nevertheless not attributable to a difference in the route of administration or the dose, the applicant for marketing authorisation for Product C is entitled to refer to the clinical documentation in respect of Product B.

So, in consideration of an application for marketing authorisation for a new Product C under Article 4.8 (a)(iii) of Directive 65/65/EEC as amended, with reference to a Product A authorised for more than 6 or 10 years, the competent authority of a Member State is entitled, with a view to granting marketing authorisation, to refer without the consent of the person responsible for marketing to data submitted in support of a Product B which was authorised within the previous 6 or 10 years under the hybrid abridged procedure laid down by Article 4.8 (a) of Directive 65/65/EEC as amended, with reference to Product A, where those data consist of clinical trials provided in order to demonstrate that Product B is safe.

2.3.3 Summary

The judgement of the Court from 29 April 2004 – Case C-106/01 gives further advice regarding essential similarity in the context of applications according Article 4.8 (a)(iii) of Directive 65/65/EEC as amended. It is not decisive in that context that all the criteria for essential similarity are satisfied with special regard to bioequivalence. Essential similarity is given, unless one or more of the differences set out in the proviso – different therapeutic use, different route or different dose – apply and unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

Additionally, the judgement stresses that there is no restart or prolongation of the data protection period of 6 or 10 years for applications for a Product B made under the proviso, by means of change of administration route or dose. These changes fall under the definition of an extension application according to Annex II of Regulation (EC) No 1084/2003.

Together with the judgement in the Generics Case, C-368/96, this means that the data protection period starts with granting of the first marketing authorisation for the original medicinal product A. Any additional therapeutic indication or route of administration or dose, respectively extension does not have any effect on the protection period of the initial marketing authorisation.

2.3.4 Relevance for Article 6 (1) and 10 (3) of Directive 2001/83/EC, as amended

Having a look at Article 6 (1) and Article 10 (3) this judgement is now included into the pharmaceutical legislation. The relevant sections are highlighted.

2.3.4.1 Article 6 (1) – 2001/83/EC

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical form, **administration routes**, presentations, as well as any variations **and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 (1).** [1]

The proviso, respectively the demand for results of appropriate pharmacological and toxicological tests and/or of appropriate clinical trials for medicinal products intended for a different therapeutic use or to be administered by different routes or in different doses has been incorporated into Article 10 (3). As well, the concept of essential similarity, interpreted less strict according to the judgement, has been considered.

2.3.4.2 Article 10 (3) – 2001/83/EC

In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), **therapeutic indications**, strength, **pharmaceutical form** or route of administration, **vis-á-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.** [1]

2.4 Judgement of the Court from 9 December 2004

Eli-Lilly Case – Case C-36/03 [9]

This judgement concerns the interpretation of Article 10 (1)(a)(iii) of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

2.4.1 The dispute in the main proceedings

Eli Lilly & Co. Ltd was granted a marketing authorisation for Prozac capsules, which was the first product containing Fluoxetine as an active ingredient in the Community in the United Kingdom in 1988. In 1992 Eli Lilly obtained the marketing authorisation for Prozac liquid in the United Kingdom and Denmark, made under the hybrid abridged application procedure. Since the liquid is per definition not essentially similar to the capsules, on account of its different pharmaceutical form, Eli Lilly submitted additional data intended to show that they were bioequivalent.

In 1999, APS applied for a marketing authorisation for Fluoxetine liquid to the MHRA under the abridged procedure under Article 10 (1)(a)(iii) of Directive 2001/83/EC claiming essential similarity to Prozac liquid. APS stated Prozac capsules as reference medicinal product approved in the United Kingdom in 1988 – authorised for more than 10 years at this date.

The MHRA took the position that APS could not use Prozac liquid as a reference product because this medicinal product had been authorised in the Community for less than ten years. APS was therefore asked to rely on Prozac capsules as and to submit the application under the hybrid abridged procedure and supply additional data in the form of a bioequivalence study comparing the two medicinal products due to lacking essential similarity.

2.4.2 Questions referred to the ECJ for a preliminary ruling

The following questions were referred to the Court for a preliminary ruling:

Can an application for a marketing authorisation for a medicinal Product C be made under the first paragraph of Article 10 (1)(a)(iii) of Directive 2001/83/EC, seeking essentially similarity to another product, Product B, in cases where:

1. Product B is a ′line extension′ of Product A but has a different pharmaceutical form or is otherwise not ′essentially similar′ to Product A.
2. Product A has been authorised for more than 6 or 10 years.
3. Product B has been authorised for less than 6 or 10 years.

2.4.2.1 Discussion

Having the same pharmaceutical form and being bioequivalent are two of the criteria that have to be satisfied when claiming essential similarity according to Article 10 (1)(a)(iii) of Directive 2001/83/EC and C-368/96 – Generics Case.

This means that the applicant is not required to provide the results of toxicological and pharmacological tests or of clinical trials. In contradiction hereto, this would be an obligation where the medicinal product is intended for a different therapeutic use from that of the other medicinal products marketed or is to be administered by different routes or in different doses as stated in the proviso.

The Court refers to its judgement in the Novartis Case, C-106/01, and states that the situation is analogous. In both cases the two products are not bioequivalent and therefore per definition not essential similar. In the Novartis Case due to different route of administration or dose, in the Eli-Lilly Case because of a different pharmaceutical form.

Since a new route of administration generally entails a change in pharmaceutical form, the same reasoning as in the Novartis Case may be followed.

The applicant for marketing authorisation for Product C may refer to the pharmacological, toxicological and clinical documentation relating to a Product B resulting from the development of the reference Product A, even if Products A and B are not essentially similar regarding their bioavailability with respect of a different pharmaceutical form and where Product B is authorised for less than 6 or 10 years. The applicant has not to rely on the proviso in such cases.

This means that an application for marketing authorisation for a Product C may be made under Article 10 (1)(a)(iii) of Directive 2001/83/EC where the application seeks to demonstrate that Product C is essentially similar to a Product B, in cases where:

1. Product B is a new pharmaceutical form of Product A, and
2. Product A, but not Product B, has been authorised for marketing in the Community for at least the six or ten year period stipulated therein.

2.4.3 Summary

The judgement of the Court from 9 December 2004, Case C-36/03, strengthens the less strict definition of essential similarity of the Novartis Case, C-106/01.

Additionally, the judgement confirms that there is no restart or prolongation of the data protection period of 6 or 10 years for further developments of medicinal products in terms of different administration routes or doses – Case C-106/01 – and pharmaceutical forms – Case-C-36/03.

In Case C-106/01 the applicant submitted additional data to prove bioequivalence between Product C and Product B – as well as Product A.

In contradiction hereto in Case C-36/03 the Court states that the applicant is not required to rely on the hybrid abridged application procedure respectively on the proviso. The application can be made under the abridged application procedure according to Article 10 (1)(a)(iii) by referring to Product A as reference medicinal product and showing essential similarity to Product B.

2.4.4 Relevance for Article 6 (1) and 10 (2) of Directive 2001/83/EC, as amended

The judgement of the ECJ Case C-36/03 confirms the judgement in Case C-106/01, meaning that the relevance for Article 6 (1) is analogous.

2.4.4.1 Article 6 (1) – 2001/83/EC

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths, **pharmaceutical form**, administration routes, presentations, **as well as any** variations and **extensions** shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations **shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 (1).** [1]

Another aspect is the implementation of Case C-106/01 within the definition of a generic in Article 10 (2):

2.4.4.2 Article 10 (2) – 2001/83/EC

(b) ′generic medicinal product′ shall mean a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivates of an authorised active substance must be supplied by the applicant. **The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.** Bioavailability

studies need not to be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate guidelines. [1]

2.5 JUDGMENT OF THE COURT from 20 January 2005

SmithKline Beecham Case – Case C-74/03 [10]

This judgement is concerning the interpretation of Article 4.8 (a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products.

2.5.1 The dispute in the main proceedings

In 1993 marketing authorisation for the medicinal product Seroxat was granted for SmithKline Beecham containing the active substance Paroxetine hydrochloride hemi-hydrate.

In 1999, the companies Synthon B.V. and Genthon B.V. submitted applications to the Competent Authority in Denmark, where a data protection period of 6 years apply, for nearly identical products containing different salts of Paroxetine, Paroxetine mesylate. The applications were made pursuant to the abridged procedure, referring to Seroxat as the reference product.

Synthon B.V. and Genthon B.V. did not submit results of clinical trials on patients since Seroxat has been already tested in healthy volunteers, but showed bioequivalence to Seroxat and supplied results from selected pharmacological and toxicological tests on animals.

The Competent authority in Denmark granted marketing authorisations for the products of Synthon B.V. and Genthon B.V. based on the conclusion that the pharmacological effect and related side effects were related solely to the Paroxetine molecule, and the salt is subordinate, assuming the same bioavailability. Additionally no differences in bioavailability were found between the two salts.

SmithKline Beecham challenged the legality of the decision by arguing that Seroxat and the products from Synthon B.V. and Genthon B.V. are not essentially similar because they contain different active substances. Furthermore, the submission of additional pharmacological and toxicological tests or clinical trials is only permitted pursuant the proviso.

2.5.2 Questions referred to the ECJ for a preliminary ruling

The responsible Danish Court decided to stay the proceedings and referred the following questions to the Court:

1. Is it compatible with Article 4.8 (a)(iii) of Directive 65/65/EC for a product to be authorised under the abridged application procedure when a salt of the active substance in the product is changed from the one used in the reference product?
2. Is it possible under the abridged application procedure to submit additional documentation in the form of certain pharmacological or toxicological tests or clinical trials either on its own initiative or at the request of national health authorities to demonstrate essential similarity to the reference product?

2.5.2.1 The second question

The abridged application procedure according Article 4.8 (a) of Directive 65/65/EC, is based on the demonstration of essential similarity. This may require the applicant to supply any additional data.

The aim to submit additional data under the abridged application procedure is to prove essential similarity. Whereas the data submitted under the hybrid abridged application procedure in the context of the proviso are designed to compensate the lack of essential similarity.

Therefore, in support of an application under Article 4.8 (a)(iii) of Directive 65/65/EEC, an applicant may, either spontaneously or at the request of the competent authority of a Member State, supply additional documentation in the form of certain pharmacological and toxicological tests or clinical trials in order to demonstrate that his product is essentially similar to the reference product.

2.5.2.2 The first question

The definition of essential similarity following the Generics Case, Case C-368/96, is, besides others, that a medicinal product is essentially similar if it satisfies the criterion of having the same qualitative and quantitative composition in terms of active principles.

The Court states that it does not follow from this criterion that there must be an exact molecular match between the active ingredients.

For the purpose of Article 4.8 (a)(iii) of Directive 65/65/EEC two medicinal products can be regarded as essential similar even if containing active substances combined with different salts.

The Court points out that another criterion for essential similarity and therefore submissions under the abridged application procedure according to the Generic Case, C-368/96, is, that a medicinal product is not regarded as essential similar if it appears, taking into account scientific knowledge, that the medicinal product for which a marketing authorisation is sought, shows significant differences from the original product as regards safety or efficacy.

Two products respectively two different salts of an active ingredient can therefore not be regarded as essential similar if they differ with respect to safety and efficacy.

Additionally, according to Regulation (EC) No 541/95 – Annex II, a new marketing authorisation application is required in the event of changes to the active substance, which, according to that Annex, includes the replacement of the active substance by a different salt.

Article 4.8 (a)(iii) of Directive 65/65/EEC must therefore be interpreted as not preventing an application for a marketing authorisation in respect of a medicinal product from being handled under the abridged procedure under that provision where that product contains the same therapeutic moiety as the reference product but combined with another salt.

2.5.3 Summary

The judgement of the Court from 20 January 2005 – Case C-74/03 once more states that the criteria for essential similarity have to be seen in a wider range. This is in line with the judgement in the Novartis Case, C-106/01, and the Eli-Lilly Case C-36/03.

Another aspect of ECJ Case C-74/03 allows an assumption about the background behind the concept of the global marketing authorisation. All possible changes to a marketing authorisation raised in Article 6 (1) that lead to a marketing authorisation belonging to the same global marketing authorisation – any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions – do not necessarily have an impact on the safety and efficacy of the pharmaceutical product. This means that pharmacological respectively toxicological tests and clinical trials don't need to be necessary in general and the repetition of tests on humans or animals can be avoided.

With respect to the aspect of ′safeguarding public health′ when talking about essential similarity and the possibility to apply for a marketing authorisation following the provisions laid down in Article 10, only those medicinal products may benefit from an abridged procedure whose safety and efficacy is at least the same as that of the medicinal products used as reference – belonging to the same global marketing authorisation.

2.5.4 Relevance for Article 10 (2) of Directive 2001/83/EC, as amended

The judgement is implemented within Article 10 (2):

2.5.4.1 Article 10 (2) – 2001/83/EC

(b) ′generic medicinal product′ shall mean a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. **The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivates of an authorised active substance must be supplied by the applicant.** The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form. Bioavailability studies need not to be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate guidelines. [1]

After having had a look at these ECJ Cases which led to the current wording of Article 6 (1) and Articles 10 (1), 10 (2) and 10 (3), and introducing the new concept of global marketing authorisation into European legislation, the impact on the regulatory environment has to be considered.

3. Concept of the Global Marketing authorisation within the regulatory environment

With the inclusion of the new concept of a global marketing authorisation into Directive 2001/83/EC, as amended the concept of ′marketing authorisation′ itself mentioned in miscellaneous other Articles of Directive 2001/83/EC, as amended besides Article 10 (1) seams not defined precise enough. It can be interpreted both as ′marketing authorisation as defined before coming into force of Article 6 of Directive 2001/83/EC′ and as ′global marketing authorisation′.

3.1 Miscellaneous Articles – Directive 2001/83/EC, as amended

There are miscellaneous Articles included in Directive 2001/83/EC, as amended, where Article 6 (1) has an impact regarding the interpretation of these Articles. These are for example Articles 8 (1) in connection with Article 25 of the German Drug Law, Article 17, Article 18, Article 28 and Article 35 besides the one mentioned in Article 6 (1) itself – Article 10 (1). In these Articles the concept of marketing authorisation is mentioned but there is no differentiation made between marketing authorisation in the conventional meaning and global marketing authorisation.

3.1.1 Article 8 (1) – 2001/83/EC

> In order to obtain an authorisation to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned. [1]

If interpreted – taking into account Article 6 (1) – this would mean that an application has to be made to receive a global marketing authorisation and to get a global marketing authorisation number allocated and that the different marketing authorisations will not be included automatically into the concept of global marketing authorisation.

This would be in accordance with the provisions laid down in Article 25 (9) of the German Drug Law, valid since 6 September 2005. This Article has been adopted, besides others, when implementing the new legislation as laid down in Directive 2001/83/EC, as amended, into national law. This Article says that an application has to be made to include a marketing authorisation into the global marketing authorisation and that a special marketing authorisation number will be allocated.

3.1.2 Article 25 (9) – German Drug Law

1. When applying for different strengths, pharmaceutical forms, application forms or devices of a medicinal product, these products can be included into a global marketing authorisation when the applicant applies for that. This even applies for changes and extensions of this marketing authorisation.
2. A common marketing authorisation number has to be allocated, additional identification to differentiate the different pharmaceutical forms or concentrations has to be included.
3. For registrations according to paragraph 24 b (1) single marketing authorisations of a reference medicinal product are handled as belonging to the same global marketing authorisation. [11]

This could mean that the marketing authorisation will no longer be handled as a single marketing authorisation standing alone by means of regulatory issues. But this item is not discussed finally until now.

3.1.3 Article 17 – 2001/83/EC

(1) Member States shall take appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 210 days after the submission of a valid application.

Applications for marketing authorisation in two or more Member States in respect of the same medicinal product shall be submitted in accordance with Articles 27 to 39.

(2) Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State, the Member State concerned shall decline to assess the application and shall advise the applicant that Articles 27 to 39 – laying down the procedures for mutual recognition and decentralised procedure – apply. [1]

If interpreting ′marketing authorisation′ with ′global marketing authorisation′ this would mean that a marketing authorisation application, that fulfils the criteria of Article 6 (1), to be part of the same global marketing authorisation, has to be submitted according to Articles 27 to 39. These Articles lay down the procedures for mutual recognition and decentralised procedure. The application can therefore not be submitted nationally in another Member State without taking into consideration the – global – marketing authorisation already granted in the EU.

3.1.4 Article 18 – 2001/83/EC

> Where a Member State is informed in accordance with Article 8 (3)(1) that another Member State has authorised a medicinal product which is the subject of a marketing authorisation application in the Member State concerned, it shall reject the application unless it was submitted in compliance with Articles 27 to 39. [1]

Taking this aspect into consideration this means that an application of a medicinal product belonging to the same global marketing authorisation would have to be rejected by the Member State, not having assessed the initial marketing authorisation application.

3.1.5 Article 28 – 2001/83/EC

(1) With view to the granting of a marketing authorisation for a medicinal product in more than one Member State, an applicant shall submit an application based on an identical dossier in these Member States. The dossier shall contain the information and documents referred to in Articles 8, 10, 10a, 10c and 11. The documents submitted shall include a list of Member States concerned by the application. [1]

If marketing authorisation means global marketing authorisation this would mean that the procedures laid down in this Article also apply for a global marketing authorisation application which may contain several marketing authorisations. A mutual recognition procedure or decentralised procedure according to Articles 27 to 39 of Directive 2001/83/EC, as amended, could than result in more than one marketing authorisation in parallel in the Community.

3.1.6 Article 35 – 2001/83/EC

(1) Any application by the marketing authorisation holder to vary a marketing authorisation which has been granted in accordance with the provisions of this Chapter shall be submitted to all the Member States which have previously authorised the medicinal product concerned. [1]

If a variation has to be made affecting all marketing authorisations belonging to the same global marketing authorisation this could lead to the assumption that this variation could be submitted once for all marketing authorisations altogether and has not to be submitted for each single marketing authorisation.

As can be seen the new concept of global marketing authorisation induces space for interpretation when trying to read Articles 8 (1), Article 17, Article 18, Article 28 and Article 35 before the background of the concept of global marketing authorisation. This shows how important it is to evaluate the impact of any new concept included in the regulatory environment. There is a difference between a marketing authorisation in the context of proceeding marketing authorisation applications including their life-cycle management and a global marketing authorisation in the purpose of data and marketing protection according Article 10 (1). Maybe the wording of Directive 2001/83/EC, as amended has to be adapted accordingly, to pay regard to these differences. It has to be defined precisely whether one Article applies for one single marketing authorisation respectively in which context the concept of global marketing authorisation applies.

In the following even more relevant issues in the field of the global marketing authorisation inducing space for interpretation are presented.

3.2 Article 10 of Directive 2001/83/EC, as amended

The provisions for data and marketing protection are laid down in Article 10 (1) of Directive 2001/83/EC. In particular for the purpose of the application of this Article the concept of global marketing authorisation has been introduced into the Directive.

3.2.1 Article 10 (1) – 2001/83/EC

> By way of derogation from Article 8 (3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical test and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community.
>
> A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product.
>
> The first subparagraph shall also apply if the reference medicinal product was not authorised in the Member State in which the application for a generic medicinal product is submitted. In this case, the applicant shall indicate in the application

form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month, a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and if necessary other relevant documentation.

The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to the authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. [1]

According to Article 2 of Directive 2004/27/EC amending Directive 2001/83/EC the periods of protection provided for in Article 1 (8), which amends Article 10 (1) of Directive 2001/83/EC, shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date of transposition referred to in Article 3 (1). Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 30 October 2005. [12]

Summary

The most relevant information included in Article 10 (1) and Article 10 (2) for reference products registered under Article 6 in accordance with the provisions laid down in Article 8 – full application – is a data protection of 8 years following the granting of marketing authorisation, another 2 years of market exclusivity where no generic medicinal product may be placed on the market and an optional prolongation of the market exclusivity up to 11 years for one or more therapeutic indication(s) with significant clinical benefit, when applied for during the first 8 years of data protection.

	Product	Indication	Data of application for MA	Marketing authorisation date	Data protection until	Bringing on the market	Market exclusivity until
1	**Reference A**	**A**		**2013**	**2021**		**2023**
2	Generic A	A	2021			2023	
3	**Reference B**	**A + B**		**2020**	**2021**		**2024**
4	**Reference B**	**A + B**		**2022**	**2021**		**2023**
5	Generic B	A + B	2021			2024	

For a Reference product A with indication A, which received marketing authorisation in 2013, a data protection period until 2021 and a market exclusivity until 2023 applies (**1**). The marketing authorisation for a Generic product A can therefore be applied for in 2021, when the data protection ends, and can be placed into the market in 2023 after the market exclusivity right for Reference A had expired (**2**). If the marketing authorisation holder for Reference A applies for another indication B to receive the marketing authorisation for Reference B within the first 8 years, before 2021, this will add another 1 year of market exclusivity until 2024 (**3**). In contradiction hereto, when the application for another indication is submitted after the first 8 years, no additional market exclusivity is granted (**4**). The marketing authorisation for a Generic product B can therefore be applied for in 2021, as well, but can be placed on the market in 2024 at the earliest, including indication B (**5**).

2001/83/EC – Article 10 (1) with regard to Article 6 (1)

When having a look on the data protection and market exclusivity periods provided in Article 10 (1), the provisions laid down in Article 6 of Directive 2001/83/EC regarding the global marketing authorisation have to be taken into consideration.

The global marketing authorisation contains the initial authorisation, any additional strength, pharmaceutical form, administration route, presentation, as well as any variation and extension thereof. Following the explanations and clarifications of the Notice to Applicants Volume 2 A – Chapter 1, this even applies to reference medicinal products authorised through separate procedures and under different name, granted to the marketing authorisation holder of the initial authorisation. [13]

In accordance with Article 6 (1) of Directive 2001/83/EC, as amended, all these presentations of a given product shall be considered as part of the same marketing authorisation for the purpose of applying the rules on data and marketing protection.

Consequently, for a reference medicinal product, the relevant date for the start of the data and market exclusivity period is the date, when the first initial marketing authorisation was granted in the Community. Any new additional strength, pharmaceutical form, administration route, presentation as well as any variation and extension has the same end point of data and market exclusivity periods. This means 8 respectively 10 years after the first marketing authorisation was granted.

	Product	Provisions of 6 (1)	Indication	Data of application for MA	Marketing authorisation date	Data protection until	Bringing on the market	Market exclusivity until
1	**Reference A**	**A**	**A**		**2013**	**2021**		**2023**
2	**Reference B**	**B**	**A**		**2017**	**2021**		**2023**
3	**Reference C**	**B**	**A + C**		**2017**			**2024**
4	**Reference D**	**B**	**C**		**2017**			**2024**
5	Generic B	A + B	A	2021			2023	
6	Generic C	A + B	A + C	2021			2024	
7	**Reference C**	**C**	**C**		**2023**			
8	**Reference E**	**C**	**C**		**2023**	**2031**		**2033**

For a Reference product A with indication A which received a marketing authorisation in 2013 a data protection period until 2021 and a market exclusivity until 2023 applies (**1**). Any additional strength, pharmaceutical form, administration route, presentation as well as any variation and extension B of Reference A, leading to Reference B, has the same end point of the data protection and market exclusivity, irrespective of the date of marketing authorisation (**2**). If the marketing authorisation holder for Reference A applies for another additional indication C to receive the marketing authorisation Reference C within the first 8 years this results in market exclusivity until 2024 (**3**). This even applies when the only indication applied for is the new additional indication and authorised through separate procedure and under a different name (**4**).

The marketing authorisation for a Generic product B can be applied for in 2021 and placed onto the market in 2023. The application can be made referencing to Reference A and B, including all strenghts, pharmaceutical forms, administration routes, presentations as well as any variations and extensions authorised for Reference product A and B (**5**). Generic C, authorised for indication A and C, can be marketed in 2024 (**6**).

If the marketing authorisation holder of Reference A applies for any new additional strength, pharmaceutical form, administration route, presentation as well as any variation and extension leading to Reference D after the protection period respectively market exclusivity rights ended for Reference A no additional data protection period is foreseen (**7**). Whereas if another company, not belonging to the same legal entity, applies for the identical new additional strength, pharmaceutical form, administration route, presentation as well as any variation and extension C and receives the first marketing authorisation according to Article 8 in 2023 for Reference product E, a data protection period until 2031 and a market exclusivity until 2033 applies (**8**).

The conclusion for the difference in applying the rules on data protection periods and market exclusivity rights according Article 10 (1) for Reference product B and C (**2/3/7**) and Reference product E (**8**) can be duly justified.

According to section 6.1.4. and 7.2 of NtA, Notice to Applicants, Volume 2 A – Chapter 1 [13], all additional strenghts, pharmaceutical forms, administration routes, presentations as well as any variation and extensions have the same endpoint of the data and market exclusivity periods, namely 8 and 10 years after the first marketing authorisation was granted (**2**). This concept of global marketing authorisation applies even if the new presentation – Reference product C – has been authorised to the same marketing authorisation holder trough a separate procedure and under a different name. No differentiation is made whether any of the changes listed in Annex II to the variation regulations are submitted as variation respectively extension application or as separate full application under the provisions of Article 8 (**4**). The 10-year period of data protection and market exclusivity can only be prolonged in the case of certain new indications, as described in the fourth subparagraph of Article 10 (1). It may be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies (**3**).

The Draft Guideline on elements required to support the significant clinical benefit in comparison with existing therapies of a new indication in order to benefit from an extended (11 years) marketing protection period [14], the so called Plus one Guideline, is in line with this statement within the NtA. According to the European Commission ′it is also possible, in addition to the Type II variation or Annex II extension, to apply for a new indication as part of a separate full stand-alone application under a new name. This new indication could benefit from the extended period of marketing protection (+1) of Article 10 (1) fourth subparagraph of Directive 2001/83/EC, but not from a full period of protection (8+2)′.

Taking into consideration section 2.3. of NtA Volume 2 A – Chapter 1, it can be concluded that a marketing authorisation holder, not belonging to the same legal entity is granted receives independent data protection and market exclusivity according Article 10 (1) for Reference product E (**8**). It says that the notion of global marketing authorisation only applies to one and the same marketing authorisation holder as for the initial marketing authorisation. Therefore, for an independent applicant the provisions of Article 10 (1) apply.

3.2.2 Article 10 (3) – 2001/83/EC

The criteria for hybrid abridged applications under Article 10 (3) are the same as they are for a marketing authorisation belonging to the same global marketing authorisation according Article 6 (1).

> In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided. [1]

Products submitted according to Article 10 (3) are therefore no generic medicinal product, besides essential similarity, as defined in Article 10 (2)(b). The provisions laid down in Article 10 (1) are linked to reference medicinal products authorised according Article 6 (1) of Directive 2001/83/EC, as amended. There is no obligation that an application has to be authorised under the provisions of Article 8 (3) to receive data protection and market exclusivity according to Article 10 (1). Therefore, Article 10 (1) should be applicable to marketing authorisations submitted under the provisions of Article 10 (3), as well.

	Product	Provisions of 10 (3) – except indication	Indication	Marketing authorisation date	Data protection until	Market exclusivity until
1	**Reference A**	**A**	**A**	**2013**	**2021**	**2023**
2	**Reference B**	**B**	**A**	**2017**	**2021**	**2023**
3	**Reference C**	**B**	**A + C**	**2023**		
4	Generic B	B	A	2017	2025	2027
5	Generic B	B	C	2019	2025	2028

For a Reference product A with indication A, which received a marketing authorisation in 2013, a data protection period until 2021 and a market exclusivity until 2023 applies (**1**). Any new active substance(s), strength, pharmaceutical form or route of administration B of Reference A, applied for in 2017 under Article 8 (3), but also fulfilling the criteria of Article 10 (3), has the same end point of the data and market exclusivity periods, which means 2021 respectively 2023 since the provisions of Article 6 respectively 10 (1) apply (**2**). Any new indication C for Reference A, resulting in Reference C, received after expiry of the data protection of the initial marketing authorisation, will not lead to an additional data protection period (**3**).

In contradiction hereto, a generic application according to the hybrid abridged application procedure laid down in Article 10 (3) for the same product as Reference A respectively B with a marketing authorisation date in 2017 would then lead to a data protection until 2025 and market exclusivity until 2027 (**4**). When applied for a new indication C within the first eight years market exclusivity ends in 2028 (**5**).

3.2.3 Article 10 (5) – 2001/83/EC

> In addition to the provisions laid down in paragraph 1 of Article 10, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. [1]

	Product	Provisions of 6 (1)	Indication	Marketing authorisation date	Data protection until	Market exclusivity until
1	**Reference A**	**A**	**A**	**2013**	**2021**	**2023**
2	**Reference B**	**A**	**A + B**	**2017**	**2021**	**2024**
3	**Reference C**	**A**	**A + C**	**2023**		
4	**Reference C**	**A**	**C**	**2024**	**2025**	**2025**
5	Generic C	A	C	2024	2025	2025
6	**Generic D**	**B**	**C**	**2024**	**2032**	**2033**
7	**Generic E**	**B**	**C + D**	**2024**	**2032**	**2034**

For a Reference product A with indication A, which received a marketing authorisation in 2013, a data protection period until 2021 and market exclusivity until 2023 applies (**1**). One additional year of market exclusivity is granted for an additional indication B approved within the first 8 years (**2**), whereas no additional protection is foreseen according to Article 10 (1) for an additional indication C after these 8 years (**3**).

If the same indication C is applied for according to Article 10 (5) a non-cumulative period of one year of data exclusivity will be granted for this indication (**4**). The same applies if the application is made form a generic company for Generic C including indication C with the relevant documentation according to Article 10 (5) (**5**).

Assumed that a Generic product D is authorised for this special indication C but for another strength, pharmaceutical form, administration route, presentation, as well as

any variation and extension B of the original Reference product A in 2024, a data protection period until 2032 and market exclusivity until 2033 applies according to Article 10 (1) (**6**). Market exclusivity until 2034 will be granted for Generic E for another indication D applied for during the first 8 years of data exclusivity (**7**).

The conclusion for the difference in applying the rules on data protection periods and market exclusivity rights according Article 10 (1) for Reference product B and C (**2 / 3**) and the Generic product D and E (**6 / 7**) can be once more duly justified with NtA Volume 2 A – Chapter 1 [13] and the so-called Plus one Guideline. [14]

The ten-year period of market protection according Article 10 (1) may only be extended by one year in the event of authorisation of new therapeutic indications representing a significant clinical benefit in comparison with existing therapies applied for within the first eight years of data protection. This new indication could benefit from the extended period of one additional year of marketing protection, but not from a full period of protection.

The only way for a marketing authorisation holder of the initial marketing authorisation for Reference A to receive any market exclusivity rights, means one year, is to apply for the additional indication under the provisions of Article 10 (5) (**4**).

In contradiction hereto a marketing authorisation holder, not belonging to the same legal entity, would receive independent data protection and market exclusivity according Article 10 (1) for the Generic product D and E (**6 / 7**).

This conclusion can be made with regard to the wording of Article 10 (5) itself, stating, that these provisions apply ′in addition′ to the provisions laid down in paragraph 1 of Article 10. This means that no non-cumulative period of one year of data exclusivity can be granted according Article 10 (5), where no initial data protection period and market exclusivity right was granted according Article 10 (1). Therefore the provisions of Article 10 (1) apply.

3.2.4 Article 10a – 2001/83/EC

> By way of derogation from Article 8 (3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions

set out in Annex I. In that event, the test and trial results shall be replaced by appropriate scientific literature. [1]

Well-established use according Article 10a refers to a specific therapeutic use as stated in NtA Volume 2 A – Chapter 1. [13]

Provided that the provisions of Article 10a apply to a special pharmaceutical form or dosage schedule of an active substance and not the active substance itself that has been in well-established use within the Community for at least 10 years, additional studies may be necessary to prove the efficacy and safety of this medicinal product applied for.

But there is no data protection period allocated for this bridging-data submitted for applications under Article 10a of Directive 2001/83/EC, as amended. Though they are necessary to obtain a marketing authorisation for a well-established use product authorised for another pharmaceutical form or dosage schedule than the well-established one.

Generic applications on a dossier based on well-established use are, according to NtA Volume 2 A – Chapter 1, acceptable because all relevant information is in the dossier of the original medicinal product. [9]

	Product	Provisions of 6 (1)	Indication	Data of application for MA	Marketing authorisation date	Data protection until	Market exclusivity until
1	**Reference A**	**A**	**A**		**2013**	**2021**	**2022**
2	**Reference B**	**B**	**A**		**2024**	**-**	**-**
3	Generic A / B	A / B	A	2021			
4	**Reference C**	**A**	**C**		**2024**	**2025**	**2025**
5	Generic C	A	D		2024	2025	2025
6	**Generic D**	**B**	**D**		**2024**	**2032**	**2033**
7	**Generic E**	**B**	**D + E**		**2024**	**2032**	**2034**

For a Reference product A with indication A, which received a marketing authorisation in 2013, a data protection period until 2021 applies (**1**). When now applying for a marketing authorisation for Reference product B for an additional strength, pharmaceutical form, administration route, presentation, as well as any variation and extension B with respect to the initial marketing authorisation for Reference product A in 2024, no data protection period and market exclusivity is foreseen. It does not make a difference whether submitting the application under the

provisions of Article 8 (3)(i) or Article 10a. In the first case the concept of global marketing authorisation applies, which means that there is no restart or prolongation of the data protection period for the initial marketing authorisation. In this special case a prolongation of market exclusivity is no longer possible since the application for a new indication is in any case too late after the 10 years of well-established use. In the second case there is no data protection for bridging data submitted under the provisions of Article 10a (**2**). Therefore the application for a Generic product A / B can be submitted in 2021 (**3**).

If an application for a well-established use active substance is submitted for a new indication C under the provisions laid down in Article 10 (5) for Reference C a non-cumulative period of one year data protection applies (**4**). The same applies if the application is made by a generic company for Generic C including indication C with the relevant documentation according to Article 10 (5) (**5**).

The following two scenarios (**6**) and (**7**) are analogous to the ones presented within chapter 3.2.5. Article 10 (5), following the same numbering-system. When a strength, pharmaceutical form, administration route, presentation, as well as any variation and extension B of a well-established medicinal product has been developed in order to be administered for a new therapeutic use, this Generic product D respectively E is granted a marketing authorisation with a data protection period and market exclusivity in accordance with Article 10 (1).

3.3 Article 23a and 24 of Directive 2001/83/EC – Sunset Clause

The provisions of the so-called Sunset Clause and the duties of the marketing authorisation holder resulting thereof are laid down in Articles 24 and 23a of Directive 2001/83/EC, as amended.

Article 24 – 2001/83/EC

(1) Without prejudice to paragraphs 4 and 5, a marketing authorisation shall be valid for five years.

(4) Any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State shall cease to be valid.

(5) When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product shall cease to be valid.

(6) The competent authority may, in exceptional circumstances and on public health grounds grant an exemption from paragraphs 4 and 5. Such exemptions must be duly justified. [1]

Article 23a – 2001/83/EC

After a marketing authorisation has been granted the holder of the authorisation shall inform the competent authority of the authorising Member State of the date of actual marketing of the medicinal product for human use in that Member State, taking into account the various presentations authorised.

There is no official statement on a common understanding how to handle the provisions of the Sunset Clause with regard to the new concept of global marketing authorisation.

Marketing authorisations granted due to a mutual recognition or decentralised procedure are handled as national marketing authorisations not taking into account Article 6 (1) of Directive 2001/83/EC at this time. They need to be marketed in the corresponding Member State in order not to cease validity.

In December 2006 the CMD(h), Co-ordination Group for Mutual Recognition and Decentralised Procedures (human), published an ′Agreement on Sunset Clause and its application to marketing authorisations granted in one or more Member State′. [15]

The problems stated were, besides others, whether the Sunset Clause will be applicable for duplicates separate from the original marketing authorisation or whether the concept of global marketing authorisation should be applied meaning that as long as the originator is marketed the Sunset Clause will not be applicable for the duplicates.

The interpretation of CMD(h) was, that the provisions of Article 24 (4), (5) and (6) should be applied individually to each separate marketing authorisation granted by a National Competent Authority even when those authorisations are duplicates.

A duplicate application is defined by reference to the first application or marketing authorisation under the provisions same dossier modules 1 to 5, same legal basis according to Directive 2001/83/EC, as amended, different trade names respectively same or different marketing authorisation holder. The above mentioned definition concerns an application for a duplicate. If a duplicate marketing authorisation is varied in a way that it deviates from the original marketing authorisation it

automatically will be outside the definition of a duplicate but would then fall under the definition of belonging to the same global marketing authorisation.

Therefore, according to CMD(h), it is not enough if the original marketing authorisation is marketed and the duplicate has not been marketed for three consecutive years. The marketing authorisation of the duplicate should then cease to be valid. The same principle apply if only the duplicate is marketed and not the original.

Additionally, the CMD(h) pointed out that the determination of the start of the three year period from the granting of the marketing authorisation should be the date when the medicinal product can be marketed by the marketing authorisation holder, taking into account e.g. the market exclusivity and other protection rules which have to be respected – please also refer to Notice to Applicants Volume 2 A Chapter 1 [9].
The agreement of the CMD(h) gives detailed information about the provisions regarding the Sunset Clause applying for duplicates as defined within this agreement.

But it is still not significant with regard to the concept of global marketing authorisation. On the one hand, one question raised was, whether the concept of global marketing authorisation should be applied for duplicates. Does this, the other way round mean, that all marketing authorisation belonging to a global marketing authorisation will not cease validity as long as one marketing authorisation out of these is marketed? On the other hand, marketing authorisations belonging to the same global marketing authorisation are falling outside the definition of a duplicate and therefore outside the scope of the agreement.

According to an EMEA-Questions- and Answer document EMEA/18079/2005 on the Application of the so-called ′Sunset Clause′ to centrally authorised medicinal products [16] ′the marketing authorisation will remain valid if at least one presentation of the marketing authorisation is placed on the market in the Community (in at least one Member State)′.

Taking into consideration the statement from the EMEA for centrally authorised medicinal products, this could lead to the assumption that marketing one presentation of the global marketing authorisation could prevent all marketing authorisations belonging to one and the same global marketing authorisation – including all marketing authorisations not marketed – from getting invalid.

Taking into consideration the changed provisions in Article 25 (9) in the German Drug Law [11] even other solutions seem to be possible in the future but are not yet discussed finally.

	Marketing authorisation	Country	Presentation	Marketing authorisation date	Date of bringing into market	Sunset provisions fulfilled – MA valid
1	**Product A**	**A**	**A**	**2010**	**2011**	**yes**
2	**Product B**	**B**	**B**	**2010**	**-**	**no**
3	EU-procedure C	A	A	2010	2011	yes
4	EU-procedure C	B	A	2010	-	no
5	**National D**	**D**	**A**	**2010**	**2011**	**yes**
6	**National D**	**D**	**B**	**2010**	**-**	**yes / no**
7	Original E	E	E	2010	2011	yes
8	Duplicate E	E	E	2010	-	no
9	**Central F**	**A**	**A**	**2010**	**2011**	**yes**
10	**Central F**	**B**	**B**	**2010**	**-**	**yes**
11	Global G	G	G	2010	2011	yes
12	Global H	G	G	2010	-	yes / no ?

Marketing authorisation A was granted in 2010 and brought onto the market within 3 years in 2011 in accordance with the provisions of Article 24. The marketing authorisation does not cease validity (**1**), whereas the marketing authorisation for Product B expires (**2**).

The same would happen to the marketing authorisation of Product A, when it would no longer be actually present on the market for a period of three consecutive years. Products resulting from a mutual recognition or decentralised procedure need to be marketed in the corresponding Member State in order not to cease validity. This means that marketing Product C in Country A (**3**) does not prevent the marketing authorisation for the same Product C in another Country B from expiring (**4**).

The application of the Sunset Clause is a national decision to be made by each concerned member state. Therefore, the situation that Presentation A for Product D is marketed (**5**), whereas Presentation B isn't (**6**), is handled different among the Member States with regard to the Sunset Clause. It depends on the procedure of allocating marketing authorisation numbers. In countries where marketing authorisation numbers are allocated for each Product D, marketing of one Presentation A prevents the other Presentation B from getting invalid (**6 yes**). That's not the case when each single Presentation A and B is allocated a marketing authorisation number (**6 no**).

According to the agreement from the CMD(h) it is not enough if Original E (**7**) is marketed and Duplicate E has not been marketed for three consecutive years. The marketing authorisation of Duplicate E should then cease to be valid (**8**).

For centrally authorised Products F all marketing authorisations will remain valid if at least one Presentation A of the marketing authorisation is placed on the market in the Community (**9 / 10**).

There are now two options for the marketing authorisations Global G and Global H belonging to the same global marketing authorisation. The marketing authorisation Global H remains valid if the concept of global marketing authorisation applies and bringing into the market of one marketing authorisation belonging to the same global marketing authorisation prevents all other marketing authorisations from getting invalid (**12 yes**); this would be in line with the procedure for centrally authorised Products F (**9 / 10**) . Global H ceases validity (**12 no**), when handled analogous to the marketing authorisation EU-procedure C or Duplicate E (**4 / 8**).

3.4 Article 24 – 2001/83/EC – Renewal

The provisions for the renewal of a marketing authorisation are laid down in Article 24 of Directive 2001/83/EC, as amended.

Article 24 – 2001/83/EC

(1) Without prejudice to paragraphs 4 and 5, a marketing authorisation shall be valid for five years.

(2) The marketing authorisation may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the competent authority of the authorising Member State.

To this end the marketing authorisation holder shall provide the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, at least six months before the marketing authorisation ceases to be valid in accordance with paragraph 1.

(3) Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal in accordance with paragraph 2. [1]

	Marketing authorisation	Marketing authorisation date	Renewal	Renewal finalised for initial MA	Harmonised Renewal date
1	**Global A**	**2010**	**2015**		
2	Global B	2012	**2017**		**possible 2015**
3	Global C	2016	**necessary ?**	**yes**	
4	Global D	2016	**necessary ?**	**no**	
5	Global E	2016	**not necessary**		
6	Global E	2016	**2021**		

All marketing authorisations Global A to E are belonging to the same global marketing authorisation according to Article 6 (1) of Directive 2001/83/EC with Global A as initial marketing authorisation.

The date of marketing authorisation for Global B (**2**) is two years later then for the initial marketing authorisation Global A (**1**). The renewal of the initial marketing authorisation A has not been proceeded and finalised. A harmonisation of the renewal dates is possible, irrespective of whether the marketing authorisations are belonging to the same global marketing authorisation or not. There is no obligation of the marketing authorisation holder to renew the marketing authorisation exactly after 5 years, the renewal date can be set before 5 years are over in agreement with the competent authorities (**2**).

The marketing authorisations for Global C and D were granted after the date of first renewal for the initial marketing authorisation. The difference for Global C and D is, that for Global C (**3**) the initial marketing authorisation Global A has already been renewed, whereas the renewal procedure is not finalised when the application for renewal has to be sent for Global D (**4**). The question for both marketing authorisations Global C and D is, whether a renewal is necessary or not. For Global C this would mean a second renewal procedure despite the finalised renewal for the initial marketing authorisation Global A, for Global D another application for renewal despite the one already submitted.

If the concept of global marketing authorisation applies regarding the provisions for renewal, this would mean that only the initial marketing authorisation Global A would have to be renewed and none of the additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions Global E thereof have to be renewed additionally (**5**). If this deduction is not in the sense of Directive 2001/83/EC the renewal of Global E is mandatory not taking into consideration the concept of global marketing authorisation (**6**).

3.5 Article 104 – Directive 2001/83/EC – PSUR 'Periodic Safety Update Report'

Once a medicinal product is authorised in the EU, even if it is not marketed, the marketing authorisation holder is required to submit a PSUR.

Article 104 – 2001/83/EC

(6) Unless other requirements have been laid down as a condition for the granting of the marketing authorisation, or subsequently as indicated in the guidelines referred to in Article 106 (1), reports of all adverse reactions shall be submitted to the competent authorities in the form of a periodic safety update report, immediately upon request or at least every six months after authorisation and until the placing on the market. Periodic safety update reports shall also be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request. The periodic safety update reports shall include a scientific evaluation of the risk-benefit balance of the medicinal product.

(8) Following the granting of a marketing authorisation, the marketing authorisation holder may request the amendment of the periods referred to in paragraph 6 in accordance with the procedure laid down by Commission Regulation (EC) No 1084/2003. [1]

Taking into consideration NtA Volume 9 – Pharmacovigilance of the European Commission [17], one PSUR may cover all dosage forms and formulations as well as indications for a given pharmacologically active substance for medicinal products authorised to one marketing authorisation holder. For any subsequent marketing authorisation the data lock points used for the PSURs for the first product should normally be used for the following joint PSURs covering the first and all subsequent products. However, the submission cycle will normally restart with the granting of a subsequent marketing authorisation.

Consequently, this would mean before the background of global marketing authorisation, that one PSUR may cover all marketing authorisations belonging to the same global marketing authorisation, using the data lock point of the initial marketing authorisation. The joint PSUR, submitted according to the cycle for the latest marketing authorisation, covers data for all previous products, belonging to the same global marketing authorisation.

Another aspect is that PSURs should be submitted taking the EU Birth Date as basic principle for all medicinal products [17]. This is the date when the first marketing

authorisation for a medicinal product is granted in the European Union for one marketing authorisation holder respectively the marketing authorisation date of the initial marketing authorisation belonging to the global marketing authorisation.

There are several circumstances where the PSUR-cycle may be amended. In certain circumstances, less frequent submissions, but at least once every five years, may be appropriate:

1. New indications, dosage forms, routes of administration or populations beyond the initial authorisation for the active substance – means marketing authorisations belonging to the same global marketing authorisation.

2. New authorisation for a medicinal product with the same qualitative and quantitative composition in terms of active principles and excipients and the same pharmaceutical form and the same route of administration as a previously authorised medicinal product, which should have been widely used in one or more Member States for the same indication(s) and should have a well-recognised efficacy and an acceptable level of safety in the same indications(s) – means Generics.

3. Where a medicinal product authorised in the EU through mutual recognition had an authorisation in the reference member state for a year or more prior to mutual recognition. [17]

	PSUR for	Provisions of 6 (1)	Marketing authorisation date	PSUR first 2 years each six months until	PSUR following two years – once a year	PSUR afterwards – three-yearly
1	**Reference A**	**A**	**2010**	**2012**	**2013 2014**	**2017**
2	Reference B	B	2011	2013	2014 2015	2018
3	**Reference A Reference B**	**A / B**	**-**	**2013**	**2014 2015**	**2018**
4	Reference C	C	2016	2018	2019 2020	2023
5	**Reference A Reference C**	**A / C**	**-**	**2018**	**2019 2020**	**2023**
6	Reference D		2013	2015	2016 2017	2020
7	**Reference A Reference D**	**A / D**	**-**	**-**	**2013 2014**	**2017**
8	Generic A	A	2022			2025
9	**Reference E**	**E**	**2022**			**2025**

All marketing authorisations Reference A to E are belonging to the same global marketing authorisation according to Article 6 (1) of Directive 2001/83/EC with Reference A as initial marketing authorisation.

For a Reference product A the PSURs have to be submitted according to the procedures laid down in Article 104 (6). This would mean for Reference product A where marketing authorisation is granted in 2010 every six months until 2012, then once a year for the following two years 2013 and 2014, and afterwards three-yearly with the first PSUR-submission in 2017 (**1**). For Reference product B the PSURs should be submitted according to Article 104 (6), too (**2**).

One PSUR may cover both marketing authorisations for Reference A and Reference B, belonging to the same global marketing authorisation. This PSUR has to be submitted according to the PSUR-cycle for Reference B, covering data for both products. (**3**). When there is a longer period between the marketing authorisation date for Reference A and the following marketing authorisations, all belonging to the same global marketing authorisation, such as Reference C (**4**), this does mean a restart of the PSUR-cycle for Reference A each time a new marketing authorisation is granted (**5**) although the PSURs for Reference A could be submitted three-yearly already.

Another possibility would be, to amend the PSUR-cycle in that way for Reference A and Reference D (**6**), that the PSUR-cycle of the initial marketing authorisation will be laid down to calculate the PSUR-submission dates for the joint PSUR. The submission of the PSUR for Reference D would then not be each six months but would follow a yearly submission interval from the beginning (**7**).

For a Generic product A the situation is well ordered in contradiction to the situation with regard to the concept of global marketing authorisation. The PSUR cycle applied can be three-yearly from the time-point of granting of the first marketing authorisation (**8**). Maybe this would be an opportunity for marketing authorisations belonging to the same global marketing authorisation such as Reference E, too, in the future (**9**).

Two facts may lead to the assumption that no restart of the PSUR-cycle is caused due to a subsequent marketing authorisation belonging to the same global marketing authorisation (**5**). Firstly the fact, that PSUR-cycles are compiled for one active substance and not for different presentations. Secondly that new indications, dosage forms, routes of administration or populations beyond the initial authorisation for the active substance are a circumstance to amend the PSUR-cycle to a less frequent submission period according to NtA Volume 9.

3.6 Annex II of Regulation (EC) No 1084/2003 - Extensions

According to Article 6 (1) of Directive 2001/83/EC, when a medicinal product has been granted an initial marketing authorisation, any extension shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the rules on data and market protection.

Extensions therefore do not restart or prolong the data and market protection period for the initial marketing authorisation.

The Community pharmaceutical legislation does not prevent a marketing authorisation holder from submitting any of the changes listed in Annex II to the variation Regulation (EC) No 1084/2003 as separate full application for marketing authorisation. [13]

This type of application has in formal to be seen as an independent application and not as a line extension. Nevertheless, the marketing authorisation obtained, will be regarded as belonging to the same global marketing authorisation prerequisite that the applicant is one and the same.

When another applicant, not belonging to the same legal entity, submits identical data, this will be handled as an independent application with regard to the rules of data and market protection.

	Applicant	Marketing authorisation	Extension to	Data submitted	Marketing authorisation date	Data protection until	Market exclusivity
1	**A**	**Reference A**			**2013**	**2021**	**2023**
2	A	Reference B	**B**		2017	2021	2023
3	B	Reference B		B	2020	2028	2030

For a Reference product A with indication A, which received marketing authorisation in 2013, a data protection period until 2021 and a market exclusivity until 2023 applies (**1**). There is no restart or prolongation of that period when the same marketing authorisation holder A applies for an extension B, neither when submitted as extension application nor as full application according to Article 8 (**2**). In contrary hereto for an independent applicant B for one and the same Reference product B, submitted as full application, the rules on data and market protection apply (**3**).

3.7 Transfer of marketing authorisation

The provisions of Article 6 (1) of Directive 2001/83/EC apply for one and the same marketing authorisation holder according to section 2.3. of NtA Volume 2 A – Chapter 1. [13]

There is no detailed clarification, neither in Directive 2001/83/EC itself, nor in the current Notice to Applicants or Guidelines which data protection and market exclusivity period applies when a marketing authorisation belonging to the same global marketing authorisation is transferred to another marketing authorisation holder.

	Product	Marketing authorisation holder	Marketing authorisation date	Data protection until	Market exclusivity until
1	**Reference A**	**A**	**2013**	**2021**	**2023**
2	Reference B	B	2020	2028	2030
3	**Reference A** and Reference B	B	**2013**	**2021**	**2023**
4			2020	2028	2030

Two marketing authorisations are granted for Reference product A (**1**) and Reference product B (**2**) for two different marketing authorisation holders A and B. Reference product A and B would belong to the same global marketing authorisation according to the provisions laid down in Article 6 (1) when applied for from one and the same marketing authorisation holder, in particular for the purpose of the application of Article 10 (1). The data protection period for Reference A lasts until 2021, for Reference B until 2028 (**1 / 2**).

There are two options for the data protection period and market exclusivity that apply when the marketing authorisation for Reference A is transferred to the marketing authorisation holder for Reference B. Either the same periods as for the initial marketing authorisation A holder apply (**3**), or the data protection periods and the market exclusivity will be the same as for the initial marketing authorisation from marketing authorisation holder B, if interpreted as subsequent marketing authorisation belonging to the same global marketing authorisation (**4**) .

In it's ′Agreement on Sunset Clause and its application to marketing authorisations granted in one or more Member State′ the CMD(h) [15] states that ′a change of ownership does not change the application of the Sunset Clause′. This means that there is no restart of the three years after granting of a marketing authorisation where the product has to be placed on the market not to cease validity. Transferred to the

provisions for data protection periods and market exclusivity according to Article 10 (1), this would lead to the assumption that the periods of the initial marketing authorisation Reference A apply, despite the periods for the initial marketing authorisation Reference B (**3**).

4. Conclusion

The introduction of the concept of **global marketing authorisation** into Article 6 (1) of Directive 2001/83/EC, as amended, seems at first sight to be an improvement in comparison to the previous Directive 65/65/EEC as amended.

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. Read in conjunction with Article 10 (1) and considering that all these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10 (1) [1], this is a clarification in comparison to the corresponding Articles 4 and 8 of the previous Directive 65/65/EEC.

The number of previous judgements of the European Court of Justice proves the assumption that this clarification of pharmaceutical legislation was highly appreciated with regard to abridged application procedures. This includes applications under the abridged application procedure according to Article 4.8 (a)(i) of Directive 65/65/EEC respectively Article 10 (1) of Directive 2001/83/EC as well as hybrid abridged application procedures according Article 4.8(a)(iii) of Directive 65/65/EEC respectively Article 10 (3) of Directive 2001/83/EC.

These judgements covered all aspects now included into Article 6 (1) respectively Article 10 (1), Article 10 (2) and Article 10 (3) of Directive 2001/83/EC, so that the regulatory requirements are now fixed within pharmaceutical legislation and do not necessarily need any further judicial review for further clarification.

One of the aspects covered is, that there is no restart or prolongation of the data protection period for further developments of an original medicinal product, with special regard to additional therapeutic indications in the Generics Case, C-368/96, additional administration routes or doses in the Novartis Case, C-106/01, and different pharmaceutical forms in the Eli-Lilly Case, C-36/03.

Additionally, the definition of the concept of essential similarity has been extended and has currently to be seen in a less strict sense.

The definition of a generic medicinal product itself, as a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies results from the judgement in the Generic Case, C-368/03. The clarification that the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy is the result of the judgement in Case C-74/03, the SmithKline Beecham Case. The influence of the Eli-Lilly Case, C-36/03, can be seen in the last paragraph of Article 10 (2) stating that the various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.

But the first impression, that the concept of **global marketing authorisation** is in any way an improvement may be deceptive.

With inclusion into Directive 2001/83/EC the meaning of miscellaneous Articles within Directive 2001/83/EC, such as Articles 8 (1) in connection with Article 25 of the German Drug Law, Article 17, Article 18, Article 28 and Article 35 besides the one mentioned in Article 6 (1) itself – Article 10 (1), is not precise enough. The concept of marketing authorisation mentioned in these Articles can be interpreted both, as ′global marketing authorisation′ or as ′marketing authorisation in the conventional meaning′. But since there is a difference between marketing authorisations in the context of proceeding applications including their life-cycle management and a marketing authorisation in the context of data protection and market exclusivity periods according Article 10 (1), this induces space for interpretation of these Articles.

Even more relevant issues touched by introducing the concept of global marketing authorisation are the ones of Article 10 (1), 10 (3), 10 (5), 10a, 23a and 24, 104, as well as Annex II of Regulation (EC) No 1084/2003 and the issue of transfer of marketing authorisation.

With respect to Article 10 (1), there is now a discrimination of a marketing authorisation holder for Reference D (**7**), who already received an initial marketing authorisation for Reference A (**1**) in contradiction to a marketing authorisation holder of Reference D, not belonging to the same legal entity. For Reference E a period of

data protection and market exclusivity is granted, whereas it's not for Reference C (**8**).

With regard to Article 10 (3), laying down the provisions for hybrid abridged application procedures, the following situation would be possible. Since the provisions laid down in Article 10 (1) are not linked to applications under Article 8 (3), it should be applicable to applications under Article 10 (3), too. This would mean, that a marketing authorisation holder for Reference A (**1**) would not receive additional data protection and market exclusivity when applying for an additional marketing authorisation belonging to the same global marketing authorisation under Article 8 (3) or 10 (3) (**2 / 3**), whereas for another applicant the provisions of Article 10 (1) apply (**4 / 5**).

In the context of applications for a new indication for a well-established use active substance under Article 10 (5) it is possible to apply for an – additional – indication and to be granted a non-cumulative period of one year of data exclusivity in contradiction to the provisions laid down in Article 6 (1) (**4**). This would be a possibility for the initial marketing authorisation holder for Reference A to receive any data protection. When a Generic product D is authorised for the same indication but for another strength, pharmaceutical form, administration route, presentation, as well as any variation and extension B of the original Reference product A the rules of Article 10 (1) apply (**6 / 7**).

Submissions under the provisions of Article 10a for well-established use active substances made from the same marketing authorisation holder as for the initial marketing authorisation under well-established use, will not be grated a data protection and market exclusivity period (**2**), whereas an independent application will fall under the provisions of Article 10 (1), when applying for another strength, pharmaceutical form, administration route, presentation, as well as any variation and extension of a well-established use substance (**6 / 7**).

Two scenarios can be drawn for marketing authorisations belonging to the same global marketing authorisation regarding Articles 23a and 24, laying down the provisions of the Sunset Clause. Firstly, a marketing authorisation remains valid if the concept of global marketing authorisation applies and bringing into the market of one marketing authorisation belonging to the same global marketing authorisation prevents all other marketing authorisations from getting invalid (**12 yes**). Secondly, it ceases validity (**12 no**) when handled analogous to marketing authorisations resulting form a mutual recognition or decentralised procedure as separate marketing authorisations (**4 / 8**).

Having a look at Renewals according to Article 24, it is a quiet similar situation. If the concept of global marketing authorisation applies, this would mean that only the initial

marketing authorisation Global A would have to be renewed and none of the additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions Global E thereof have to be renewed additionally (**5**). If this deduction is not in the sense of Directive 2001/83/EC, the renewal of Global E is mandatory (**6**).

Another issue, the submission of PSURs according Article 104 covering data for all marketing authorisations belonging to the same global marketing authorisation, is not regulated in detail. The question is, whether each new marketing authorisation restarts the PSUR-cycle for a Reference product A (**3 / 5**) or whether the PSUR-cycle of the initial marketing authorisation will be laid down to calculate the PSUR-submission dates for the joint PSUR (**7**). Maybe the same procedure as for generic products – three-yearly submission of PSURs – would be an opportunity for marketing authorisations belonging to the same global marketing authorisation (**9**).

Regarding extension applications falling under Annex II of Regulation (EC) No 1084/2003, there is quite a discrimination between applicants. For an applicant who already received a marketing authorisation this extensions falls under the provisions of Article 6 (1) (**2**), whereas for another applicant, not belonging to the same legal entity, submitting identical data, the rules of data and market protection apply (**3**).

The aspect of a possible transfer of a marketing authorisation, which would per definition belong to the same global marketing authorisation when submitted from one and the same marketing authorisation holder, brings another point for discussion. When a marketing authorisation for Reference A is transferred to the marketing authorisation holder for Reference B, either the same periods as for the initial marketing authorisation A holder apply (**3**), or the data protection periods and the market exclusivity will be the same as for the initial marketing authorisation from marketing authorisation holder B (**4**).

In summary, it can be ascertained, that when reading and interpreting Articles 10 (1), 10 (3), 10 (5) and 10a before the background of the new concept of global marketing authorisation, the main question arising is, how to apply the provisions for data protection and market exclusivity for these different application procedures. With regard to Articles 23a, 24 and 104 the question is how to apply the different requirements and time lines of the Sunset Clause, for Renewals and for PSUR-submissions.

5. Outlook

The impact on the regulatory environment when including the new concept of global marketing authorisation into pharmaceutical legislation has not been considered in detail when adopting Directive 2001/83/EC, as amended.

According to Article 86 of Regulation (EC) 726/2004 [18], 'the Commission shall publish at least every ten years a general report on the experience acquired as results of the operation of the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC' – laying down the procedures for mutual recognition and decentralised procedure.

This general report should not only cover the experience gained with these marketing authorisation procedures.

It should also be addressed for parts within Directive 2001/83/EC where there is too much space for interpretation.

There is no doubt about the need for clarification of the issues raised in the previous chapters of this Master Thesis. But regulatory future will show who will address these issues and gives detailed information about a common understanding. Either the CMD(h), the EMEA or, when not addressed in time, the European Court of Justice.

Finally, pharmaceutical legislation, respectively Directive 2001/83/EC, will have to be amended once more, due to the experiences made.

6. Summary

With coming into force of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended a new regulatory concept has been introduced into the European legislation – the **global marketing authorisation** according to Article 6 (1).

When a medicinal product has been granted a marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same **global marketing authorisation**, in particular for the purpose of the application of Article 10 (1).

The object of this Master Thesis is to examine this new concept of global marketing authorisation according Article 6 (1) of Directive 2001/83/EC, as amended, from two different perspectives: on the one hand with regard to the legislation previous to Directive 2001/83/EC, as amended and several judgements from the European Court of Justice, based on that legal basis, on the other hand it's impact on miscellaneous Articles within the current regulatory environment as laid down in Directive 2001/83/EC, as amended.

When adopting Directive 2001/83/EC, the European Parliament and the Council followed several decisions from the European Court of Justice that have been issued on the basis of the legislation into force at the time of the ruling. There are four judgements that had a significant influence leading to the current wording of Articles 6, 10 (1), 10 (2) and 10 (3) of Directive 2001/83/EC, as amended, and a common understanding of regulatory aspects such as essential similarity, data protection, or the abridged application procedure for medicinal products. These judgements are the Generics Case, C-368/96, the Novartis Case, C-106/01, the Eli Lilly Case, C-36/03 and the SmithKline Beecham Case, C-74/03.

For the purpose to reach a common understanding about the regulation of the above mentioned regulatory aspects, the incorporation of the concept of global marketing authorisation according Article 6 (1) into pharmaceutical legislation, in connection with the adoption of Article 10 (1), Article 10 (2) and Article 10 (3), seems to be obvious.

Nevertheless, it implicates basis for discussion, since the impact on the regulatory environment has to be considered. This means, it has to be seen in context with all other regulatory requirements being relevant for a marketing authorisation as defined

before coming into force of Article 6 (1) of Directive 2001/83/EC, as amended and not restricted to Article 10 (1).

The meaning of miscellaneous Articles within Directive 2001/83/EC, such as Articles 8 (1) in connection with Article 25 of the German Drug Law, Article 17, Article 18, Article 28 and Article 35 is currently not precise enough. The concept of marketing authorisation mentioned in these Articles can be interpreted both, as ′global marketing authorisation′ or as ′marketing authorisation in the conventional meaning′. But since there is a difference between marketing authorisations in the context of proceeding applications including their life-cycle management and a marketing authorisation in the context of data protection and market exclusivity periods according Article 10 (1), this induces space for interpretation of these Articles.

Even more relevant issues touched by introducing the concept of global marketing authorisation are the ones of Articles 10 (1), 10 (3), 10 (5), 10a, 23a and 24, 104, as well as Annex II of Regulation (EC) No 1084/2003 and the issue of transfer of marketing authorisation. When reading and interpreting Articles 10 (1), 10 (3), 10 (5) and 10a before the background of the new concept of global marketing authorisation the main question arising is, how to apply the provisions for data protection and market exclusivity for these different application procedures. With regard to Articles 23a, 24 and 104 the question is, how to apply the different requirements and time lines of the Sunset Clause, for Renewals and for PSUR-submissions.

There is no doubt that there is a need for clarification of these issues either by the CMD(h), the EMEA or, when not addressed in time, the European Court of Justice. Maybe, at the end, pharmaceutical legislation, respectively Directive 2001/83/EC, will have to be amended once more due to the experiences made.

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B. Sträter
22 June 2006, Bonn

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

Sabine Wägele