

Data Protection for the Development
of Known Drug Substances -
Changes with the Review of EU Legislation

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vorgelegt von

Dr. Arno Wiehe

aus Bonn

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Betreuerin und 1. Referentin: Oberregierungsrätin A. Büttrich

Zweite Referentin: RA Dr. H. Wachenhausen

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Abbreviations

AMG	Arzneimittelgesetz
CP	Centralised Procedure [in Regulations EC/2309/93 and EC/726/2004, respectively]
DP	Decentralised Procedure [in Directive 2004/27/EC]
EC	European Community
ECJ	European Court of Justice
EEC	European Economic Community
EGA	European Generic Medicines Association
EMA	European Medicines (Evaluation) Agency
EU	European Union
ICH	International Conference on Harmonisation
MCA	Medicines Control Agency [former name of the competent authority of the UK responsible for medicinal products]
MRFG	Mutual Recognition Facilitation Group
MRP	Mutual Recognition Procedure [in Directive 2004/27/EC and 2001/83/EC]
NtA	Notice to Applicants
PIP	Paediatric Investigation Plan [in the Paediatric Proposal]
SPC	Supplementary Protection Certificate
TRIPS	Agreement on Trade Related aspects of Intellectual Property rights
VfA	Verband forschender Arzneimittelhersteller
WTO	World Trade Organisation

1. Introduction

When the process of reviewing the pharmaceutical legislation of the European Union (EU) started, in the beginning termed 'Review 2001', it had five basic aims:

- to guarantee and further improve the high level of public health
- to complete the single market
- to increase transparency
- to favour competitiveness of the industry
- and to prepare for the EU enlargement¹

Based on these goals of assuring a high level of protection of public health in a political environment which favours the development of a competitive pharmaceutical industry and promotes the operation of the internal market this process eventually resulted in the adoption of three Directives and a Regulation in March 2004.² These Directives and the Regulation amend and replace the current legislative texts, respectively.

In the field of medicinal products for human use³ the review particularly aimed at the revision of the two fundamental texts: The Directive 2001/83/EC and the Regulation EEC/2309/93. As a result Directive 2001/83/EC was amended by two texts:

Directive 2004/24/EC: amending Directive 2001/83/EC as regards traditional herbal medicinal products.

Directive 2004/27/EC: revising diverse provisions of Directive 2001/83/EC

The old Regulation EEC/2309/93 was replaced by Regulation EC/726/2004.

A Regulation is directly binding and applicable in all Member States of the EU,⁴ i.e. Regulation EC/726/2004 has entered into force on the 20th day following its publication in the Official Journal of the EU on the 30.04.04.⁵ A Directive on the other hand needs to be transposed into the legal order of the Member States. For this, the Member States have been given a time limit until the 30.10.2005.⁶ In Germany for

¹ Erkki Liikanen, member of the EU Commission at a Press Conference in Brussels, 18 July 2001, cf. KINTZEL, 2004.

² Directives 2004/27/EC, Directive 2004/28/EC, Directive 2004/24/EC, and Regulation EC/726/2004.

³ In parallel, the basic text for medicinal products for veterinary use, Directive 2001/82/EC, was reviewed resulting in the amending Directive 2004/28/EC. Centrally authorised products for veterinary use are also covered by Regulation EC/726/2004.

⁴ NtA Vol. 2a, chapter 1, p. 21.

⁵ Regulation EC/726/2004, Art. 90 (1).

⁶ Directive 2004/27/EC, Art. 4.

example, this transposition will take place with the 14th amendment to the Arzneimittelgesetz (AMG). For certain provisions of Directive and Regulation specific different time limits are given.⁷

The Directives and the Regulation encompass a variety of provisions concerning all aspects of medicinal products for human use, i.a.:⁸

- Changes in the marketing authorisation procedure for pharmaceuticals, i.a. a new kind of marketing authorisation procedure is introduced, the Decentralised Procedure (DP).
- New indications are named for which the Centralised Procedure (CP) for marketing authorisation becomes mandatory; also the possibilities where the CP is optional are expanded.
- Clearer definitions are provided for 'borderline' products situated between cosmetics, medicinal products, medicinal devices and food.
- The market access for generic medicinal products is facilitated.
- Specific regulations for biological medicinal products and 'biogenerics'.
- The importance of pharmacovigilance aspects is stressed; new pharmacovigilance provisions are included in the Directive and the Regulation.
- In the future, the renewal of a marketing authorisation has to be applied for only once. On the other hand, a 'sunset clause' is introduced, i.e. marketing authorisations which have not been used for three years become invalid.
- The data protection periods for medicinal products are harmonised.
- Specific provisions for herbal medicinal products are introduced.

The provisions contained in the Directives and the Regulation will have a great impact on the marketing authorisation and the development of medicinal products by the pharmaceutical industry.⁹ Due to the long transition periods for certain regulations the regulatory affairs managers in industry will have to deal for a long time with old *and* new provisions. Especially with respect to data protection, significant changes are introduced with the new legislation, that have to be enclosed in the strategic consideration of originators as well as manufacturers of generic medicinal products.

⁷ Cf. below chapter 3 of this thesis.

⁸ BOGAERT, 2004.

⁹ HORTON, 2004a; HORTON, 2004b.

In this context the present thesis aims to contribute to these strategic considerations by giving a basic overview about the present provisions on data protection and exclusivity rights, by describing the changes occurring with the new legislation and finally by pointing out some general options for pharmaceutical development in this legislative framework.

Besides patent protection the data protection (i.e. the protection of the pre-clinical and clinical data of the originator of a medicinal product towards referencing by a third party, details see chapter 2) is the central component by which the market access of generic medicinal products is prevented for a defined period and thus, it is also a main incentive for research and development. Data protection and related exclusivity rights are especially important for active substances whose patent protection has or is about to expire.

A lot of research in the pharmaceutical industry is dedicated to the development of known active substances, i.e. substances that have already obtained a marketing authorisation for a certain indication and are benefiting from patent and/or data protection. Sometimes new fields of application are discovered for these known active substances, more often a new strength, a new route of administration or a new pharmaceutical form more convenient or more suitable for certain patient groups is developed. These extensions of existing marketing authorisations are commonly referred to as 'line extensions'. With respect to these line extensions data protection is a central issue and precisely here the new legislation brings a drastic change, though this change has already been suggested in recent judgements of the European Court of Justice (ECJ). Thus, the aspect of data protection for the development of known drug substances will be a central issue of this thesis.

The interdependence of data protection and pharmaceutical development is also acknowledged in a study undertaken for the European Commission by the consulting agency Charles River Associates ('Innovation in the pharmaceutical sector', published in November 2004). This report analyses the reasons for the decline in 'innovative productivity' in the EU in recent years and discusses possible options for improving this. With respect to generic competition the report says:

"First, the increased importance of the branded period will provide an incentive to channel resources into R&D for new products that will gain acceptance quickly in order to keep a competitive product portfolio. On the other hand, it will increase the

incentive to focus on incremental innovations that will lead to a further period of market exclusivity.”¹⁰

Later on the report continues: “Data protection and market exclusivity period: Granting extended data protection and market exclusivity periods for significant new indications of already existing products or products for certain groups of patients, such as children, increases the returns to innovation and hence the incentive to invest in R&D in such products.”¹¹

As said in the abovementioned text, the granting of exclusivity rights is also an effective measure to promote the development of the pharmaceutical industry and to pursue public health ends. Exclusivity rights can be used to 'channel' research and development, to encourage the finding of new medicinal products for specific indications or patient groups (e.g. the Orphan Drug Regulation EC/141/2000). Therefore, these exclusivity rights have also to be taken into account when analysing data protection and discussing possible options.

The most recent development in this direction is a Regulation on medicinal products for paediatric indications. The final proposal for such a Regulation has been submitted by the European Commission to the European Parliament in September 2004.¹²

This proposal which is inspired by similar regulations in the United States contains important data and market exclusivity provisions. Though changes to the text of the proposal are likely to be made during the further process of legislation which will be finished approximately in 2006 the provisions contained in it shall nevertheless be discussed in this thesis, mainly because - as a Regulation - it will immediately be legally binding to all Member States of the EU. Thus, if the process is finished in 2006 its provisions will become legally binding earlier than some parts of the Regulation EC/726/2004.

Finally, this thesis will concentrate on medicinal products for human use and will mainly be concerned with the European legislation with only few references made to national legislation.

¹⁰ CRA REPORT, 2004, p. v.

¹¹ CRA REPORT, 2004, p. v-vi.

¹² PAEDIATRIC PROPOSAL, 2004. The proposal was published on the 29.09.2004, cf. also: LIESE, 2004 and THROM, 2004.

2. General Overview on Intellectual Property and Data Exclusivity Rights and Status Prior to the Review of EU Legislation

The aim of protecting and improving public health is an integral part of the basic treaties of the EU. It is the guiding idea behind the EU legislation related to medicinal products.

Another central concern of the EU legislation is the freedom of the internal market, i.e. the free movement of persons, goods, capital, and services in the Community.

For the question of data protection a third aspect is important: the right to property, especially intellectual property, which is also protected by the founding legislative texts of the EU.

Art. 17 of the Charter of the Fundamental Rights of the European Union says:

Right to property

1. Everyone has the right to own, use, dispose of and bequeath his or her lawfully acquired possessions. No one may be deprived of his or her possessions, except for in the public interest and in the cases and under the conditions provided for by law, subject to fair compensation being paid in good time for their loss. The use of property may be regulated by law insofar as is necessary for the general interest.
2. Intellectual property shall be protected.¹

In an international context intellectual property is also protected by a number of conventions and agreements, namely the TRIPS-Agreement by the WTO members in 1996 (Agreement on Trade Related aspects of Intellectual Property rights).² Art. 39.3 of this agreement is concerned with the data exclusivity for pharmaceuticals and obliges countries to protect against unfair commercial use of confidential data on new chemical entities submitted by companies to obtain approval for marketing new drugs from a regulatory agency.

The international importance and the discussion about the TRIPS agreement in developing countries or those not belonging to the three ICH regions³ is due to the fact, that compliance with the TRIPS obligations is linked to the trade advantages con-

¹ Charter of the Fundamental Rights of the European Union, cf. europa.eu.int/comm/justice_home/faq/rights/wai/faq_rights_en.htm.

² General information on http://europa.eu.int/comm/internal_market/index_en.htm.

nected with the WTO membership.⁴ Thus, the relationship between intellectual property rights, free trade, the safeguarding of public health and the fundamental human rights is a field of constant discussion.⁵

In this chapter, the main regulations on intellectual property protection related to medicinal products for human use in the EU shall be presented providing an overview on the status prior to the review of EU legislation. First, patent protection and its extension, the Supplementary Protection Certificate (SPC), will be presented followed by a discussion on data protection and related exclusivity rights such as the market exclusivity for Orphan medicinal products.

2.1 Patent Protection

The primary tool for the protection of scientific and technical innovations with a potential for a commercial application is the patent. To obtain a patent the applicant has to submit a description of the details of his invention together with the respective claims to the patent office where the eligibility of the invention for patenting is examined. After the end of the assessment the patent is published and becomes accessible to other interested parties. The two main criteria for patenting are novelty and the possibility of commercial application, discoveries without a commercial application are not eligible for patenting.

To be distinguished from 'normal' patents are utility and design patents (Gebrauchs- and Geschmacksmuster), the main difference being the degree of novelty, that is higher for patents and lesser for utility patents. The design of a product, its aesthetic aspects may be protected by a design patent, e.g. the layout of the packaging of a medicinal product.

Novelty and commercial applicability are assessed by the patent office on submission of the patent. Detrimental to the novelty of a patent is any mentioning of the

³ ICH: International Conference on Harmonisation. Forum for Cooperation of the Regulatory Agencies and the corporations of the pharmaceutical industry of Europe, USA and Japan to formulate harmonised guidelines for the development of pharmaceuticals.

⁴ CORREA, 2002.

⁵ FARACIK, 2002; PUGATCH, 2004; DE RIDDER, 2003.

idea/the concept underlying the patent in publicly available resources, e.g. existing patents, publications, or public oral presentations.⁶

After the patent has been granted, the patent protection lasts usually for 20 years during which increasing patent fees have to be paid.

The patent holder may take legal proceedings (via civil law) against anybody who is using his idea commercially. Though the patent owner is entitled to *prohibit* the commercial use of his invention by others *the patent does not in itself allow the patent owner to actually use his invention*. The actual use of a patent can be restricted by law or other regulations as e.g. in the field of medicinal products where a product may only be used after being assessed and evaluated by the regulatory agencies. While the *commercial use* of a patent can be prevented by the patent owner *research* on this idea is possible, indeed often the publication of a patent - once it has been granted by the patent office - is a decisive stimulus for research by other companies. In Europe, the publication of a patent has to be made no later than 18 month after its filing with the patent office.

Naturally, the patent owner can grant others a licence to make use of his patent.

A main problem with respect to medicinal products are the studies required from a generic medicinal product in order to obtain a marketing authorisation (bioequivalence studies, cf. below). Under the current law the conduction of these studies and the manufacturing of medicinal products for these studies was an infringement to patent law. Therefore these studies were usually performed outside Europe. With the review of EU pharmaceutical legislation an important new provision addressing this issue was introduced [Roche-Bolar-Clause, cf. below, Art. 1 (8) of Directive 2004/27/EC]. Whereas, the *submission* of an application for marketing authorisation *and its subsequent evaluation* by the regulatory agency and also *the granting of a marketing authorisation* are - according to the EU Council and the EU Commission - considered as administrative acts not infringing patent protection.⁷ However, no regulation exists as of which date prior to the end of patent protection the submission of a marketing authorisation application for a generic medicinal product is possible. Additionally the submission of an abridged (generic) marketing authorisation application requires reference to be made to the data of the original medicinal product and this would be prohibited by any existing data protection, regardless of whether there

⁶ Sometimes, e.g. in the USA there is a certain time-frame after the publication (in a journal) during which a patent relating to the idea expressed in the publication may still be applied for.

is still patent protection or not. In some EU Member States even the submission of samples to the regulatory agencies in the course of a marketing authorisation application is considered as patent infringement. There are other differences with respect to patents for medicinal products between the Member States. A Roche-Bolar-like clause allowing research and development of generic medicinal products exists in Portugal, Poland, Hungary and Slovenia. Generic research and development is explicitly prevented in UK and the Netherlands.⁸

The scope of properties eligible for patenting has been considerably widened in recent years. As the patent law is still the main tool to guarantee market exclusivity for a certain time, there is a strong tendency to protect as much innovation as possible by patents. A list of the European Generic medicines Association (EGA)⁹ shows which aspects were eligible for patenting in the 1980s and how this list has been expanded since 1990:

In 1980:

Primary uses

Processes and intermediates

Bulk forms

Simple formulations

Composition of matter

Since 1990 the following aspects were added:

Expansive numbers of uses

Methods of treatment

Mechanism of action

Packaging

Delivery profiles

Dosing regimen and range

Dosing route

Combinations

Screening Methods

Chemistry Methods

Biological Target

Field of use

⁷ Council's reasons relating to Common Position 61/2003.

⁸ PERRY, 2004.

Thus, depending on the position patent protection is either a "guarantor for therapeutic innovation" or a tool to perpetuate the monopoly for a certain medicinal product.¹⁰

As mentioned above, the patent protection period is 20 years starting from the filing date of the patent with the patent office. In order to secure the invention from the beginning the patent filing of a new active substance will be made at a very early stage of the pharmaceutical development process, long before the marketing authorisation application is filed or even long before clinical trials have been performed. This will result in the dilemma that once the marketing authorisation is obtained already a significant part of the patent protection period has expired. Today, the average remaining patent protection period after marketing authorisation is about 10 years.¹¹ In other research fields the time between patent filing and the time where the return of investment starts is much shorter. This is aggravated by the substantial costs associated with the development of a new medicinal product, costs that may well reach several hundred million Euros for certain frequent indications. The largest part of these costs accumulates during the clinical development.

2.1.1 Extension of Patent Protection: Supplementary Protection Certificate

In 1992, the EU introduced a Supplementary Protection Certificate (SPC) for medicinal products in order to provide a compensation for the long development time and high development costs for medicinal products.¹²

The following rationale is quoted from the introduction to Regulation EEC/1768/92:

"Whereas at the moment the period that elapses between the filing of an application for a patent for a new medicinal product and authorization to place the medicinal product on the market makes the period of effective protection under the patent insufficient to cover the investment put into the research;"

and further:

"Whereas the duration of the protection granted by the certificate should be such as to provide adequate effective protection; whereas, for this purpose, the holder of

⁹ EGA, 2004, citing LARSON, 2001.

¹⁰ EGA, 2004; VFA, 2004.

¹¹ VFA, 2004.

both a patent and a certificate should be able to enjoy an overall maximum of fifteen years of exclusivity from the time the medicinal product in question first obtains authorization to be placed on the market in the Community;”

According to this Regulation (Art. 6), the SPC shall be granted to the holder of the basic patent or his successor in title. As the SPC is an extension of the rights of the underlying patent, it is said, that “the certificate shall confer the same rights as conferred by the basic patent and shall be subject to the same limitations and the same obligations” (Art. 5). The other limitation to the SPC is the marketing authorisation: Art. 4 restricts the protection only to the product that is covered by the underlying market authorisation and to those uses as a medicinal product authorised before the expiry of the certificate, i.e. new indications developed during the duration of the SPC are also protected until the end of the SPC.

The SPC must be lodged within a period of six month after the first granting of a marketing authorisation *within the community* (!) as a medicinal product.¹³

Art. 13 of Regulation EEC/1768/92 determines the duration of the additional protection term: The time between the date of the filing of the patent and the date of the first marketing authorisation of the product in the EU is reduced by five years. The remaining period is granted as the additional protection term, but if this time is longer than five years it is cut off to a maximum of five years.

The effect of this Regulation may best be visualised in a small diagram:

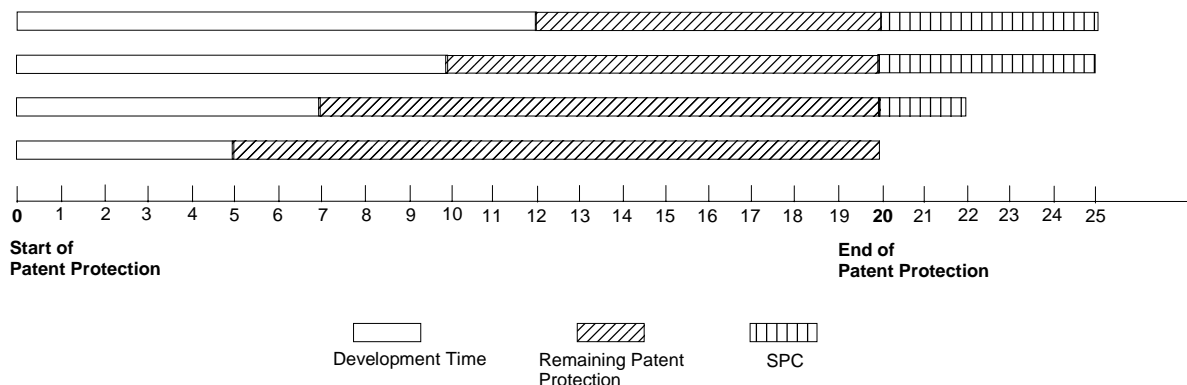


Fig. 1: Effect of patent protection and SPC.

¹² Regulation EEC/1768/92.

¹³ If the first marketing authorisation is a marketing authorisation as a *veterinary* medicinal product this authorisation nevertheless starts the six month term, i.e. if later on the medicinal product is authorised for human use an SPC is no longer possible, cf. ECJ Case C-31/03.

This diagram illustrates that the combined period of remaining patent protection and SPC after marketing authorisation amounts to a maximum of fifteen years. The 'optimal' effect of the SPC is achieved after a development period of 10 years, which is about the average development time from a new active substance to a medicinal product. For development times longer than 10 years there is only a partial compensation via the SPC.

Finally, it is to be noted that the marketing of a generic medicinal product is not possible prior to the end of the patent protection term or the SPC. As of which time prior to the end of either period a marketing authorisation for a generic medicinal product may be filed is not regulated.

2.2 Data Protection

As indicated by the above discussion of the SPC the longer the development time the more important become additional exclusivity provisions. This is the main reason why the importance of data protection has increased in recent years.¹⁴

What is data protection?

To obtain a marketing authorisation for a medicinal product the applicant (the pharmaceutical company) has to submit extensive data packages (pre-clinical and clinical studies) to the competent authorities in order to prove quality, safety, and efficacy of the product. Data protection means that the regulatory agency may not - for a defined period of time - without the explicit consent of the originator of that data make reference to these data when assessing the marketing authorisation application for a medicinal product of another company which is identical or similar to the original medicinal product.

Thus, data protection is not a *prohibition* for the generic company to apply for a marketing authorisation as the generic company may of course apply for a marketing authorisation *based on its own data*¹⁵ (as long as no other exclusivity rights, e.g. a patent hinder this) but given the enormous costs associated with the studies on

¹⁴ DE RIDDER, 2003.

¹⁵ If a generic company would indeed pursue this path ethical questions would arise (e.g. unnecessary testing in human subjects).

safety and efficacy of a medicinal product *in practice* data protection accounts for an effective market monopoly for the time of its duration.

Nevertheless, this protection is different from patent protection it is more a factual/economical hindrance to other companies than a legal one.

One of the origins of data protection lies in the protection of biotechnical innovations as patenting for these products was originally more difficult than today.¹⁶

There are significant differences in the specific periods of data protection between the three ICH regions as well as compared to other (economically) important regions. The data protection period in the USA is up to 5 years, 5 years in Australia and New Zealand, 4-10 years in Japan, and 6 years in China to name only a few examples.¹⁷

Also, within the EU there are different data protection periods (based on old provisions in Directive 2001/83/EC and Regulation EEC/2309/93).

Centrally authorised products

For medicinal products that have been authorised via the centralised procedure (CP) the answer is simple: Those medicinal products benefit from a data protection period of 10 years according to Art. 13 (4) of Regulation EEC/2309/93. According to Art. 74 of the Regulation EEC/2309/93 this provision entered into force on the 01.01.1995. Therefore it is only during the present and the following years that an increasing number of medicinal products authorised via the CP fall out of data and patent protection. Thus, the question of generic medicinal products derived from centrally authorised products is relatively new.

Nationally authorised products

The data protection periods for nationally authorised medicinal products are given in Art. 10 of Directive 2001/83/EC.

This Article regulates under which circumstances the applicant is not required to provide the results of pre-clinical and clinical tests and when reference may be made to the data of the originator.

¹⁶ IDRAC 'GENERIC', 2004. Today, generic medicines to biotechnological products, officially termed 'similar biological medicinal products' pose a specific problem to the regulatory agencies, cf. BRAKE, 2004.

¹⁷ DE RIDDER, 2003.

Prior to listing the data protection periods a short summary of Art. 10 shall be given because all discussions about generic medicinal products are centered around this provision.

Art. 10 names three cases in which the applicant is not required to provide data on the safety and efficacy of the medicinal product:

- **Art. 10 (1a) (i)**: if the medicinal product for which a marketing authorisation is sought is "essentially similar" to a medicinal product authorised in the Member State concerned and if the originator has given his consent (the so-called '**informed consent application**').

- **Art. 10 (1a) (ii)**: if no data have to be provided because the medicinal product has a "well-established medicinal use". This well-established use has to be proved by a detailed scientific, critical bibliography (so-called '**bibliographic or well-established use application**'). The term 'well-established medicinal use' is to be understood as detailed in the Annex I of Directive 2001/83/EC.¹⁸ Roughly, well-established use means a systematic and documented use as a medicinal product for at least 10 years in the EU for the specific therapeutic use for which the application is made.¹⁹

- **Art. 10 (1a) (iii)**: if the medicinal product is 'essentially similar' to a product that has been authorised within the community for not less than 6 years and is marketed in the Member State for which the application is made. For products of the concertation procedure (the predecessor of the CP) this time is extended to 10 years.²⁰ EU Member States can extend the 6-year data protection term to 10 years for all medicinal products marketed in their territory. Additionally, the Member States are allowed not to apply the 6-year protection term beyond the date of expiry of the underlying patent.

Art. 10 (1a) (iii) describes the real '**generic or abridged application**'. In practice, the criterion of 'essential similarity' with the authorised product (reference product) has to be proved by clinical studies showing bioequivalence.

¹⁸ The current version of the Annex I to Directive 2001/83/EC is given in Directive 2003/63/EC, cf. also NtA Vol. 2a, chapter 1.

¹⁹ NtA Vol. 2a, ch. 1, p. 8.

²⁰ Marketing authorisation according to Art. 4 of Directive 87/22/EEC (revoked).

The last paragraph of Art. 10 (1a) (iii) contains a reservation ('**proviso**') for cases in which the medicinal product for which 'essential similarity' is claimed is

- meant for a different indication
- administered in a different form
- administered in a different dose

than the already marketed original medicinal product.

In these cases the results of pre-clinical and clinical studies have to be provided in order to fill the gap between the marketing authorisation of the original medicinal product and the product for which a marketing authorisation is sought (bridging studies). This sort of application is referred to as the '**hybrid abridged application**'.

It should be noted that according to Art. 10 there are *two kinds of studies* which are to be provided in case of an abridged application. The difference between these two is relevant with respect to the later discussion of judgements of the ECJ:

- Studies may be required in order to prove 'essential similarity' with the reference product.
- Studies may be required with respect to the 'proviso' in order to fill the gap between the data of the original medicinal product (reference product) and the product for which a marketing authorisation is sought. Also in this case there is still 'essential similarity' which is why only *additional studies* are required and not a complete set of data but nevertheless the products *are no longer in all aspects 'essentially similar'* (pharmaceutical form, dose, and indication).²¹

So, based to Art. 10 of Directive 2001/83/EC the following data protection periods apply in the EU Member States:²²

- 10 years for medicinal products authorised via article 4 of Directive 87/22/EC (the ex-concertation procedure)
- 10 years (by single decision) for other medicinal products in Belgium, Germany, France, Italy, the Netherlands, Sweden, the United Kingdom and Luxembourg;
- 6 years in Austria, Denmark, Finland, Ireland, Portugal, Spain, Greece and in the new Member States Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, Slovak Republic and Slovenia (as well as Norway and Iceland).

²¹ ECJ C-74/03 'SmithKline Beecham' (20.01.2005).

²² NtA Vol. 2a, ch. 1 and IDrac Database.

Art. 10 determines the starting point of the data protection term as the date of the first marketing authorisation in the EU ("... authorized within the Community ..."). Unfortunately, the mutual recognition procedure (MRP) for marketing authorisation which is regulated in Directive 2001/83/EC²³ usually runs for a considerable period (sometimes 3-4 years), thus in practice a loss of data protection is inevitable as the data protection period already starts with the first authorisation in a Member State. Unlike the MRP, the CP has the decisive advantage that the granted marketing authorisation is instantly valid in all Member States.

One issue often arising with respect to the Mutual Recognition Procedure is the question about the end of the data protection period in cases where a marketing authorisation has been obtained in several Member States with *different* regulations, i.e. with data protection periods of 6 and 10 years, respectively. This question is addressed in the NtA: "... if the data protection period is equal in all the CMS(s), no problem will arise. If, however, the protection period in the CMS is longer than in the RMS, mutual recognition in the CMS is not possible before the expiry of the longer period."²⁴ The same position is expressed in a report of a meeting of the Mutual Recognition Facilitation Group (MRFG).²⁵

Finally, the effect of the combination of patent protection, SPC and data protection term shall again be visualised in a small diagram (modified according to STRÄTER, 2004²⁶):

²³ MRP: The marketing authorisation is applied for in one Member State and is later acknowledged by other Member States via a procedure regulated in Directive 2001/83/EC, in the end the applicant obtains a number of national marketing authorisations.

²⁴ NtA Vol 2a, ch. 1, p. 14.

²⁵ Annex 7 of EMEA/CPMP/2347/03.

²⁶ STRÄTER, 2004; STRÄTER, 2005.

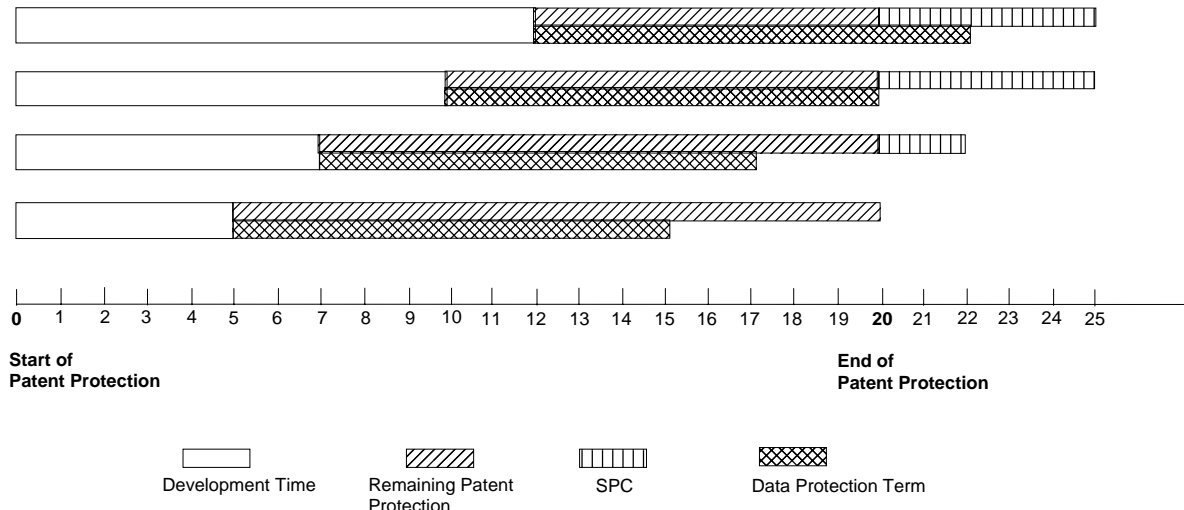


Fig. 2: Effect of patent protection, SPC, and data protection period (exemplified for a data protection period of 10 years).

As can be seen from this diagram, the data protection period has usually expired before the end of patent protection or patent protection + SPC. So, data protection becomes relevant for medicinal products with a long development time prior to marketing authorisation. And it is of course important if there is no more patent/SPC protection for example for further developments of a medicinal product (a new strength, a new formulation) issued years after the first marketing authorisation.

2.2.1 Data Protection in the Context of the Interpretation of Art. 10 of Directive 2001/83/EC

Important explanations regarding the data protection provisions, especially Art. 10 of Directive 2001/83/EC, are given in the Notice to Applicants Vol. 2a, chapter 1 from February 2004, which summarises the status immediately before the passing of the new legislation.²⁷ Further clarifications with respect to Art. 10 are given in four judgements of the ECJ and in statements by the MRFG. In particular, these texts address the question to what extent extensions and further developments of an original medicinal product benefit from data protection.

A central term in this discussion is the term 'line extension' for which a short discussion shall be given.

²⁷ NtA Vol. 2a, ch. 1.

2.2.1.1 Line Extensions and Extension Applications

The majority of medicinal products appearing newly on the market are not new in the sense of containing a hitherto unknown active substance. Mostly, they are based on an active substance that is already known and for which a marketing authorisation is sought based on bibliographic data (well-established use) or referring to the data of existing medicinal products. This referring to existing data may either be done by generic companies or by the originator of these data if he wants to extend the present marketing authorisation to a new indication, a new pharmaceutical formulation (e.g. with improved pharmacokinetics and pharmacodynamics), a new strength or combinations thereof. Naturally, there is a strong interest by the generic companies to obtain marketing authorisations covering also these new indications, formulations or strengths.

These new developments in the 'life-cycle' of a medicinal product are commonly referred to in the regulatory context as line extensions which characterises them already from their name as continuations of an existing product line. Depending on the national legislation related to medicinal products these line extensions are regulated differently. In certain cases those line extensions were also attributed a new data protection period. In Germany, for example, if the marketing authorisation was granted for a different indication, strength or form of administration as a *new* marketing authorisation according to § 29 (3) AMG and if the medicinal product was subject to the automatic prescription regulated in § 49 AMG then in certain cases an extension of the data protection period was granted.²⁸ Naturally, this is very attractive for originators as this opens the opportunity to extend the effective market exclusivity by life-cycle management.

The first legal definitions related to line extensions are given in the two variation Regulations from 2003 which refer to medicinal products authorised either based on Directive 2001/83/EC (Regulation EC/1084/2003) or on Regulation EEC/2309/93 (Regulation EC/1085/2003). However, the term 'Extension Application' which is defined in these Regulations is used in a narrower sense than that in which line extension is usually understood.

²⁸ BÜTTRICH, 2004. It should be noted that this data protection for certain line extensions was granted only until the judgement in ECJ case C-368/96 'Generics' was issued, cf. also below.

The variation Regulations discriminate between three kinds of 'changes' to a medicinal product:

Minor Variations: For these, a further discrimination into type IA and IB is made. The two types are extensively defined in Annex I of each of the two Regulations.

Extension Applications: In Annex II of each Regulation 'changes' are named which are such that they can no longer be treated in the course of a variation procedure but need to be applied for with a new marketing authorisation application, i.e. as an Extension Application, these include:

- Changes of the active substance which *do not have* a significant effect with respect to safety and efficacy (use of a different salt or ester, use of a different isomer).
- Changes of strength, pharmaceutical form or route of administration (e.g. change of the release rate or of bioavailability.)²⁹

Major Variations: This type of changes - named type II - covers all variations to a medicinal product that are not minor variations and that are not to be handled as Extension Applications.

This can be summarised in the following picture (neglecting solely national authorisation procedures and exceptions such as the transfer of the marketing authorisation holder):

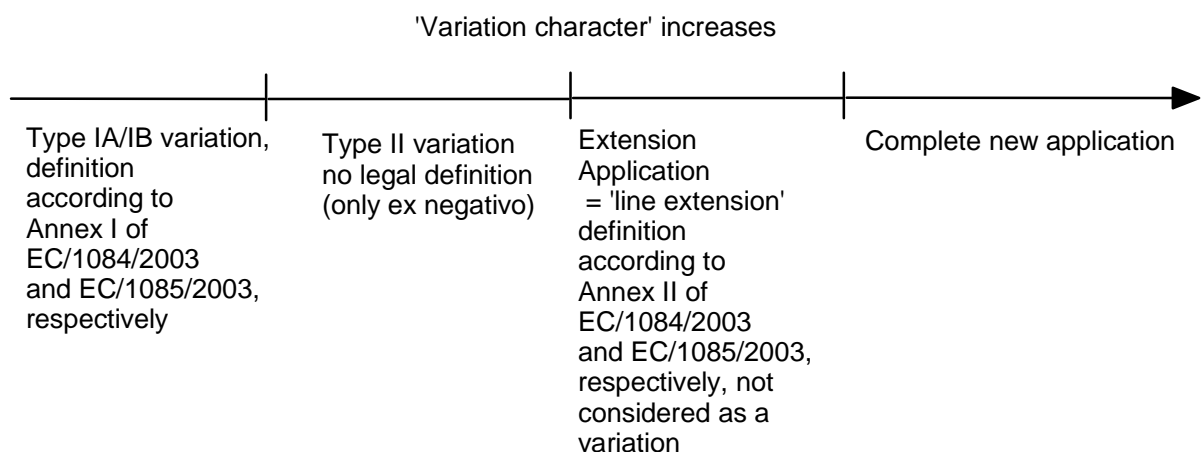


Fig. 3: Variations in relation to Extension Applications and new applications.

It should be noted that the introduction of a new indication which in the pharmaceutical industry would be regarded as an extension of a product line is - according to the

variation Regulations - only a type II variation. Additional instructions for the demarcation between type II variations and Extension Applications are given in a guideline of the EU Commission.³⁰

As illustrated in Figure 3 Extension Applications possess a double character: Formally, they are regarded as new applications but concerning the content of the dossier and the innovation aspect, they are positioned below a new marketing authorisation. This is one reason why they were only in some cases granted a new data protection period. Nevertheless, the dossier of an Extension Application is a full dossier to which reference may be made according to Art. 10 (1a) (i) und (iii) of Directive 2001/83/EC. One important condition for an Extension Application is that it has the same invented name as the medicinal product to which it is related.³¹

2.2.1.2 Art. 10 of Directive 2001/83/EC According to the 'Notice to Applicants'

After this clarification of the terms 'line extension' and 'Extension Application' now the specific questions of data protection related to abridged applications according to Art. 10 (1a) (i) and (iii) shall be discussed.

According to the Notice to Applicants the following conditions must be met in order to submit an abridged application:

1) A full dossier has to be at the disposal of the competent authorities.³² Only to such a full dossier reference may be made with consent of the originator or without his consent after the end of the data protection period.³³

Examples for such full dossiers are:

- bibliographic applications for well-established use products
- applications combining bibliographic data with new data of the applicant
- full applications of the originator of a medicinal product
- line extensions of this product filed as new marketing authorisation applications

²⁹ Annex II of Regulation EC/1084/2003 and Regulation EC/1085/2003.

³⁰ NtA Vol 2C, Guideline on the categorisation of extension applications (EA) versus variation applications (V) (October 2003).

³¹ NtA Vol. 2a, ch. 1; Annex II of Regulation EC/1084/2003 and Regulation EC/1085/2003.

³² This implies for example that a medicinal product requesting 'essentially similarity' to a medicinal product authorised via the CP also has to use the CP; cf. NtA Vol. 2a ch. 1, p. 11. But this requirement has been modified with Regulation EC/726/2004; cf. also below.

³³ NtA Vol. 2a, ch. 1.

2) The medicinal product to which reference is made with an abridged application "is marketed" in the Member State for which the application is made.³⁴ The term "is marketed" must be understood as authorised. If a valid marketing authorisation still exists but the product is no longer marketed the marketing authorisation for a generic product may still be granted provided the non-marketing was not based on reservations related to quality, safety, and efficacy of the original medicinal product. It is also sufficient if the original product is marketed at the time of filing of the generic product. If the marketing authorisation is then revoked by the applicant, the generic product may nevertheless be given a marketing authorisation (ECJ Case C-223/01).

3) The medicinal product for which the marketing authorisation is made is 'essentially similar' to the reference or original medicinal product.

The following definitions are given in the NtA:

Original medicinal product: the product to whose full dossier reference is made and whose data protection has expired.

Reference medicinal product: the product marketed in the Member State for which the application is made. In this Member State the reference medicinal product can be authorised for less than 6/10 years. This reference medicinal product can be of different strength or have a different pharmaceutical form or can be approved for other indications or have other excipients than the original medicinal product.

Usually, this reference medicinal product is used for the bioequivalence studies with the medicinal product of the abridged application.

Unfortunately, the terms 'essentially similar' and 'generic medicinal product' are not defined in the old version of Directive 2001/83/EC. Therefore, the interpretation of these terms has taken place during legal proceedings at the ECJ concerning the positions of originators and generic pharmaceutical companies.³⁵

A central role in this discussion has the judgement in the ECJ case C-368/96 'Generics'.³⁶ This judgement takes up positions that were already formulated at a meeting of the Council of Ministers on the occasion of accepting Directive 87/21/EEC.

³⁴ This requirement has been eliminated with Directive 2004/27/EC.

³⁵ As a consequence Directive 2004/27/EC contains a definition of generic medicinal product and has eliminated the term 'essential similarity'.

³⁶ ECJ C-368/96 'Generics'.

According to this judgement a medicinal product is 'essentially similar' to an original or a reference medicinal product if

- it possesses the same qualitative and quantitative composition in terms of active principles/substances,
- has the same pharmaceutical form
- it is bioequivalent (which is to be proven by comparative studies)

A complementing basic requirement is that the product in question and the original or the reference product do not differ significantly with respect to safety and efficacy.

According to the NtA the first two requirements must be understood in a broader sense: Other esters, salts and derivatives which contain the same active moiety are to be considered as 'essentially similar' (as long as they do not differ with respect to safety and efficacy).³⁷ Also, for the application of the concept of 'essential similarity' all oral solid pharmaceutical forms for immediate release are to be regarded as the 'same pharmaceutical form'.

In summary, based on the judgement in case C-368/96 the NtA states: A generic marketing authorisation "... may be issued for all therapeutic indications and all dosage forms, doses and dosage schedules already authorised for the originator product, even if some of those indications, dosage forms, doses, had been authorised for a period shorter than 6/10 years."³⁸ (Today the following terminology is in use: pharmaceutical form = dosage form, strength = dose and posology = dosage schedule).

The NtA continues:

"The medicinal product to which essential similarity is claimed must be either the original medicinal product or a line extension thereof. Referring to the abovementioned Court Case [C-368/96], the requirement for authorisation for at least 6/10 years in the Community does not apply to line extensions used as reference products beyond the 6/10 years data exclusivity period of the original medicinal product."³⁹

The same position is taken by the MRFG, the forum of the regulatory agencies of the EU Member States in a publication from 1999 (last updated July 2002). This paper discusses on what kind of application a 'line extension' may be based relating to the

³⁷ Cf. below judgement in ECJ case C-74/03.

³⁸ NtA Vol. 2a, ch. 1, p. 14, partially citing the judgement of ECJ C-368/96.

³⁹ NtA Vol. 2a, ch. 1, p. 15.

Annex II of the old variation Regulation EC/541/95 (the predecessor of Regulation EC/1084/2003):⁴⁰

- **An abridged application in accordance to Art. 10.1.a)iii), 1st paragraph of Dir. 2001/83/EC**, when the line extension is essentially similar to a reference product already approved in the Member States where the application is made.

Note: the reference product must be authorised for at least 6/10 years in the Community and the authorisation should be based on a complete dossier in each Member State or a line extension of a complete dossier. **However, referring to the ECJ case C368/96 of 3 December 98, the requirement for authorisation for at least 6/10 years in the Community does not apply to line extensions used as reference products beyond the 6/10 years data protection period of the originator product of that line.**

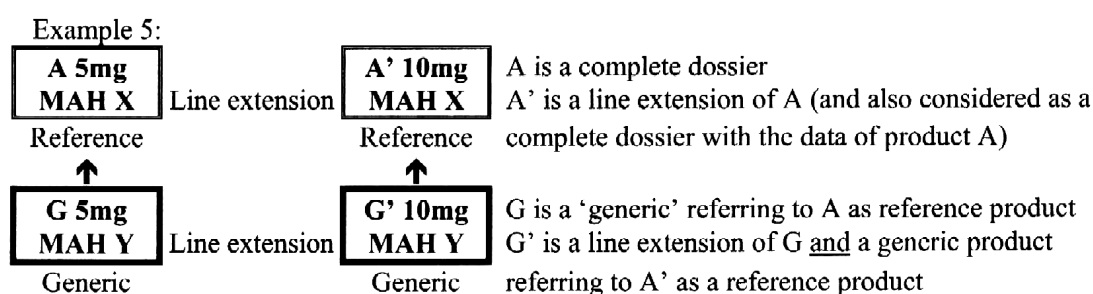


Fig. 4: Picture taken from MRFG, 2002.

Thus, the generic line extension may be based on the data contained in the dossier of the line extension of the originator (which is considered as a full dossier, cf. above).

In spite of this judgement and its interpretation there was no expressly decision on whether indeed all later modifications (all 'line extensions') of an original medicinal product are exempt from benefiting from a new data protection period, once the data protection period for the original medicinal product has expired.⁴¹ This question has again become relevant with the development of line extensions encompassing new innovative pharmaceutical forms (e.g. liposomal formulations, nanoparticulate formulations, formulations with certain excipients of biological origin such as protein nano-

⁴⁰ MRFG, 2002.

⁴¹ And indeed, new data protection periods have been granted in some cases, cf. above the example at the beginning of ch. 2.2.1.1. In Germany, the granting of a new data protection for line extensions under certain conditions was abandoned after the 'Generics' judgement. After this judgement no further data protection for line extensions was granted, neither for new indications (this is directly derived from the 'Generics' judgment) nor for new pharmaceutical forms or strengths. Eventually, this practice was confirmed by further judgements of the ECJ, cf. the discussion below.

particles). Some of these formulations require extensive clinical studies even if they are formally 'only' extensions of existing marketing authorisations.

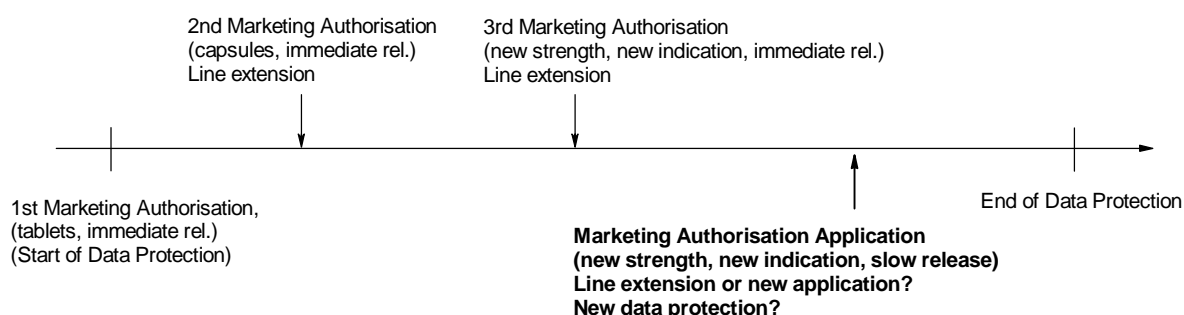


Fig. 5: Problem of data protection for innovative line extensions/Extension Applications.

Three judgements relating to data protection for pharmaceuticals have been issued by the ECJ since the beginning of 2004: ECJ case 106/01 (29.04.2004), case 36/03 (09.12.2004) and case 74/03 (20.01.2005). Two of them expressly deal with line extensions. In the following, the content of these judgements shall therefore shortly be summarised.

2.2.1.3 ECJ Case 106/01 (29.04.2004) 'Novartis'

Background:⁴² The pharmaceutical company Novartis (or, more specific, the company Sandoz which is now part of Novartis) had obtained a marketing authorisation for the medicinal product 'Sandimmun' (active substance: cyclosporin in the pharmaceutical form of a *macroemulsion*). As a line extension to this product whose patent and data protection period had expired, a new medicinal product 'Neoral' was developed showing improved absorption and administration properties (active substance: cyclosporin, in the pharmaceutical form of a *microemulsion*). The marketing authorisation application for 'Neoral' was made according to Art. 4.8 (a) (i) of Directive 65/65 as amended [the wording of this Article being the same as for Art. 10 (1a) (i) of Directive 2001/83/EC], i.e. as an informed consent application based on 'essential similarity' making reference to the data of 'Sandimmun'. Additionally, under the 'proviso' [today Art. 10 (1a) (iii) of Directive 2001/83/EC] data of new studies and clinical

tests were provided in order to account for the differences between 'Neoral' and 'Sandimmun', that is, the marketing authorisation application for 'Neoral' was filed as a hybrid abridged procedure.⁴³ 'Neoral' obtained its first marketing authorisation in the EU in 1994.

In 1999, the company SangStat obtained two national marketing authorisations from the competent authority of the UK (the MCA) for the medicinal product 'SangCya' (active substance: cyclosporin, in the pharmaceutical form of a *nanodispersion*) based on a hybrid abridged procedure according to the proviso in Art. 4.8 (a) (iii) of Directive 65/65 as amended [= Art. 10 (1a) (iii) of Directive 2001/83/EC]. 'Sandimmun' which had been authorised within the EU for at least 10 years served as the reference product. 'SangCya' has been developed independently of 'Sandimmun' or 'Neoral', is protected by US patents and is not identical with 'Neoral'. Data were provided for 'SangCya' to show the 'essential similarity' as well as a superbioavailability compared to 'Sandimmun'. In addition, studies were presented aimed at showing bioequivalence between 'Neoral' and 'SangCya' (marketed in the USA). For the marketing authorisation of 'SangCya' the British competent authority also made reference to data submitted by Novartis for the marketing authorisation application for 'Neoral'.

Novartis applied for judicial review of the decision of the MCA to grant these marketing authorisations and – after this application was dismissed - lodged an appeal before the Court of Appeal. Novartis stated:

- The MCA unlawfully cross-referred to the Neoral file (cross-reference problem).
- The MCA erred in finding that SangCya is essentially similar to Sandimmun, i.a. because it is not bioequivalent (essential similarity problem).
- The MCA infringed the principle of non-discrimination between Novartis and SangStat in terms of the authorisation procedure (non-discrimination problem).

The counter arguments of the MCA were:

- It is entitled to cross-refer to all information in its possession in assessing the safety of a product for which marketing authorisation is sought.

⁴² ECJ C-106/01 'Novartis'.

⁴³ In this case, though, the application was filed as a hybrid abridged procedure with *informed consent of the first applicant*, i.e. a combination of Art. 10 (1a) (i) with the proviso of Art. 10 (1a) (iii). If this is possible was part of the legal proceedings, cf. below.

- Questions of essential similarity "enjoy a margin of discretion in deciding such issues such as whether two products have the same pharmaceutical form"⁴⁴. Bioequivalence is not always required to demonstrate essential similarity.
- There was no infringement of the non-discrimination principle as Novartis and SangStat were not in the same position.

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

- 1) Is the national competent authority ever entitled to cross-refer, without consent, to data of a product B (not authorized for 6/10 years) when examining the marketing authorisation for a product C which makes reference to a product A, which has been authorised for 6/10 years?
- 2) If this is the case, may such cross-reference be made where
 - Product B was authorised under the hybrid abridged procedure with reference to product A?
 - the data to which reference is made were, as indicated by the national competent authority, necessary to obtain the marketing authorisation for product B and to demonstrate the safety of product B ?
- 3a) Does the final subparagraph (the proviso) apply only to applications according to Art. 4.8 (a) (iii), i.e. for generic/abridged applications or also for applications according to Art. 4.8 (a) (i), i.e. informed consent applications?
- 3b) Is essential similarity a prerequisite for an application under the proviso?
- 4) Can products be essentially similar if they are not bioequivalent, and if so when?
- 5) What is the meaning of 'same pharmaceutical form' in the judgement of ECJ Case C-386/96 ('Generics')? Is it the same pharmaceutical form if products are provided as macroemulsion, microemulsion or nanodispersion?
- 6) Is it consistent with the principle of non-discrimination to require full clinical data for product B but – after having examined the data in support of product B – not to require the same for product C?

The ECJ gave the following answers:

Regarding question 4: As bioequivalence is interpreted e.g. in the Generics judgement as a prerequisite for essential similarity, two products cannot be considered as

⁴⁴ ECJ C-106/01 'Novartis', paragraph 22 (p. 6).

essentially similar for the purpose of an informed consent or a generic application if they are not bioequivalent.

Regarding question 5: The term pharmaceutical form is not defined in the relevant community legislation. According to relevant information, i.e. the European Pharmacopoeia, the term pharmaceutical form must take into account the form in which the pharmaceutical product is presented by the manufacturer and the form in which it is administered. So, though different particle sizes are eventually formed in the solution taken by the patient, this does not mean, these forms may not be treated as the same pharmaceutical form for the application of the informed consent or the generic application, provided that there are no differences in scientific terms.

Regarding question 3a: The hybrid abridged procedure (the proviso) applies for both, the generic and the informed consent application, as the argument for restricting the clinical trials and tests for an application to the amount needed, i.e. to avoid an ethically and scientifically inappropriate repetition of clinical testing holds in both cases.

Regarding question 3b: It is stated, that if essential similarity in a strict sense would be required for a hybrid abridged application, then the proviso would be useless as it could never be applied for different routes or doses and would be restricted only to cases, where the *same* pharmaceutical product is intended for a new indication. Thus, the concept of 'essential similarity' is a prerequisite for the proviso, but *it is not required* that the product for which marketing authorisation is sought, is *in all aspects* essentially similar to the reference product. There may be differences with respect to dose, pharmaceutical form or indication, as stated in Art. 4.8 (a) (iii) [today Art. 10 (1a) (iii) of Directive 2001/83/EC].⁴⁵

Regarding question 1 and 2: As stated in the 'Generics' Judgement, the marketing authorisation for a product essentially similar to a reference product is given for all therapeutic indications of the reference product, also for those issued for less than 6/10 years. Those indications are not attributed a further protection period of 6/10 years. The same holds for other routes or doses. With respect to the proviso, such a further development of the original or reference medicinal product is to be regarded in the same way, regardless of whether it differs from the original with respect to route of administration, dose or only by being used for a new indication. So, in this context, it is not decisive if the products A and B satisfy all criteria of essential similarity or not. As stated in question 3b, a strict requirement of essential similarity would

hinder nearly all cross-referring for different routes or doses. The ECJ summarises this by saying:

"Therefore, the applicant for marketing authorisation for a medicinal product may refer to that documentation where the products resulting from the 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."⁴⁶

"If product B resulting from the development of the 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."⁴⁷

So, in considering a marketing authorisation application for product C the national competent authority is entitled to cross-refer without consent to data submitted for product B, authorised via the hybrid abridged procedure, which has not been authorized for 6/10 years.

Regarding question 6: The ECJ takes the position of the MCA by saying that the principle of non-discrimination is not infringed because during the marketing authorisation process of product C product B is already authorised and its safety and efficacy has already been proven.

The judgement in case C106/01 strengthens the position of the EU Commission (as expressed in the NtA) as well as of the MRFG that there is no data protection for line extensions, i.e. the period is started only once with the first marketing authorisation for the original medicinal product. The judgement also stresses that the term 'essential similarity' is not to be understood in a narrow sense when comparing the products in question (especially relating to the original medicinal product and its line extensions).

2.2.1.4 ECJ Case 36/03 (09.12.2004) 'Approved Prescription Ltd.'

Background: The company Eli Lilly had obtained a marketing authorisation for the medicinal product 'Prozac' (active substance: fluoxetine, in the pharmaceutical form

⁴⁵ Cf. also BÜTTRICH, 2004.

⁴⁶ ECJ C-106/01 'Novartis', paragraph 64 (p. 13).

of capsules) in the UK in 1988. In 1992 Eli Lilly achieved a marketing authorisation for a line extension of 'Prozac' termed 'Prozac Liquid' (active substance: fluoxetine, in liquid form). 'Prozac Liquid' was authorised based on a hybrid abridged procedure using 'Prozac' as the reference product. In the course of this hybrid abridged procedure new data were provided to show the bioequivalence of the two medicinal products.

In 1999 the company Approved Prescription Ltd. (APS) applied in the UK for a marketing authorisation for 'Fluoxetine liquid 20 mg/5 ml' according to an abridged procedure following Art. 10 (1a) (iii) of Directive 2001/83/EC stating that their medicinal product was essentially similar to 'Prozac Liquid' and that the reference medicinal product ('Prozac' capsules) has been authorised for at least 10 years.

The Medicines and Healthcare products Regulatory Agency (MHRA) took the position that it is not possible to make reference to 'Prozac Liquid' because this medicinal product had not been authorised for at least 10 years. Therefore, the MHRA required APS to rely on 'Prozac' capsules and to submit additional data (in a hybrid abridged procedure) to show bioequivalence between 'Fluoxetine liquid' and 'Prozac' capsules. APS applied for judicial review of the decision of the MHRA before the High Court of Justice. The High Court decided to stay the proceedings and referred the following questions to the ECJ:

Can an application for a marketing authorisation for a medicinal product C be made under Art. 10 (1a) (iii) of Directive 2001/83/EC, seeking to prove 'essential similarity' to another medicinal product B in cases where:

- Product B is a line extension of Product A but has a different pharmaceutical form compared to A or is in other aspects not 'essentially similar' to product A, and where
- Product A has been authorized for 6/10 years, and
- Product B has been authorized for less than 6/10 years?

The ECJ gave the following answer:

The court refers to its judgement in the 'Novartis' case (C-106/01) and states that the situation is analogous to the 'Novartis' case as here also the original medicinal product and the variant are not essentially similar insofar as they have a different pharmaceutical form. So, as in the 'Novartis' case the applicant for a marketing authorisation for product C may refer to the documentation of product B which is a devel-

⁴⁷ ECJ C-106/01 'Novartis', paragraph 65 (p. 13).

opment of product A, even if A and B are not essentially similar with respect to a different pharmaceutical form and where B has not been authorized for 6/10 years. The ECJ also refuses the position of the MHRA that in such cases the applicant has to rely on the proviso for his marketing authorisation application.

This judgement of the ECJ confirms in a general way, that there is no data exclusivity for further developments of existing medicinal products. In contrast to case C106/01 where the second applicant - at least partly - provided bridging data, in this case it is stated that the applicant when seeking a marketing authorisation for his product C is not required to use the hybrid abridged procedure but may use the 'normal' abridged procedure according to Art. 10 (1a) (iii) by referring to the original version of a medicinal product A as the reference product and by demonstrating essential similarity in comparison with the line extension product B.

Again the ECJ stresses that with respect to 'essential similarity' a full congruence in all aspects is not required. A short analysis of the judgement in case ECJ C-36/03 is titled: "Prozac – depressing news for data exclusivity".⁴⁸ This analysis questions if the judgement does not in general abandon the concept of 'essential similarity' for abridged generic applications.

In the opinion of the author of the present thesis the 'argumentation chain' of the ECJ is different:

- An original medicinal product and its line extension are often *not in all aspects* 'essentially similar' as defined in 'Generics' (with the exception of medicinal products where only a new indication is added without any changes to dose and/or pharmaceutical form).
- The proviso for the hybrid abridged procedure is intended exactly for these cases to bridge the differences between the original medicinal product and the line extension.
- Though not in all aspects 'essentially similar' the two products are still linked by their data basis, the line extension (partly) resting on the data of the original medicinal product, thus, the line extension is not a new medicinal product.
- According to the 'Generics' judgement a *generic medicinal product may be authorised for all indications of the original medicinal product*, whether authorised for 6/10 years or not. There is no new data protection period for indications developed later after the first marketing authorisation.

- The same holds for a new strength or a new pharmaceutical formulation, also for these line extensions there is no new data protection period.
- Therefore, a generic product may use these line extensions as reference medicinal products for the bioequivalence studies, while with respect to the authorisation for 6/10 years referring to the original medicinal product.

2.2.1.5 ECJ Case 74/03 (20.01.2005) 'SmithKline Beecham'

In contrast to the two ECJ cases mentioned above, this case is not related to line extensions, but to the aspect of data exclusivity in connection with the abridged procedure according to Art. 4.8 (a) (iii) of Directive 65/65 [= Art. 10 (1a) (iii) of Directive 2001/83/EC].

Background:⁴⁹ The company SmithKline Beecham plc. had obtained the marketing authorisation for the medicinal product 'Seroxat' (active substance: paroxetine hydrochloride hemi-hydrate) in 1993.

In 1999 the companies Synthon BV and Genthon BV submitted mostly identical applications for marketing authorisation to the competent Danish authority for 'Paroxetine Synthon' and 'Paroxetine Genthon' (the data exclusivity period in Denmark is 6 years, cf. above). These applications were made pursuant to the abridged procedure with 'Seroxat' as the reference product. 'Paroxetine Synthon/Genthon' contained paroxetine but not as hydrochloride hemi-hydrate but as mesylate.

In addition to the documentation required under the abridged procedure, Synthon and Genthon submitted animal tests. The competent Danish authority requested further information. Synthon/Genthon did not submit results of clinical trials on patients as the use of Synthon/Genthon in humans was already documented indirectly by the bioequivalence study with 'Seroxat'.

The experts of the competent Danish authority as well as external experts said that the relevant pharmacological effects and side effects are solely related to the paroxetine moiety and that the counterion of the salt is of subordinate importance. Additionally, no differences with respect to bioavailability were found.

The competent Danish authority subsequently granted the marketing authorisation for 'Paroxetine Synthon/Genthon'.

⁴⁸ LINKLATERS IP NEWSLETTER, 2005.

⁴⁹ ECJ C-74/03 'SmithKline Beecham'.

SmithKline Beecham plc challenged the legality of this decision, arguing that 'Seroxat' and 'Paroxetine Synthon/Genthoon' are not essentially similar because they contain different active substances. Furthermore, it was argued that the submission of additional data is only permitted pursuant to the proviso.

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

- 1) Is it compatible with Art. 4.8 (a) (iii) [= Art. 10 (1a) (iii)] to grant a marketing authorisation for a medicinal product under the abridged procedure, if the product submitted for marketing authorisation and the reference product contain the same active substance hence in the form of a different salt?
- 2) Is it possible to use the abridged procedure, if the applicant, either on its own initiative or on request of the competent authority submits additional data (non-clinical or clinical tests) to demonstrate the essential similarity of his product?

The ECJ gave the following answers:

Regarding question 2: The basis of the abridged procedure is the demonstration of essential similarity between a new medicinal product and a reference product. This often requires the supplying of additional data in any form.

The supplying of additional data according to the 'normal' abridged procedure and the hybrid abridged procedure serve different aims: in the first case those data serve to prove the existence of essential similarity in the latter case they serve as a compensation for a lack of essential similarity.

Therefore, in support of an application according to the abovementioned article, the applicant may supply any kind of data (on request or spontaneously) to demonstrate essential similarity.

Regarding question 1: The ECJ points out that "It does not follow from the criterion of essential similarity as laid down by the Court in *Generics* that there must be an exact molecular match between the active ingredients."⁵⁰

Thus, two substances may still be regarded as essentially similar with respect to Art. 4.8 (a) (iii) though they contain the active substance in the form of a different salt.

⁵⁰ ECJ C-74/03, 'SmithKline Beecham', paragraph 33 (p. 7).

The court points out, that the central issue behind 'essential similarity' is not the protection of innovator companies (that is achieved via the 6/10 year data exclusivity periods) but the safeguarding of public health.⁵¹ The Court refers to the *Generics* definition of essential similarity that contains the provision, that two medicinal products may be regarded as essentially similar if they have same qualitative and quantitative composition in terms of active principles/substances, the same pharmaceutical form and if they are bioequivalent, "*unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.*"⁵²

So, the decisive question is, whether the substitution of one salt for another poses a risk to public health (i.e. if they differ with respect to safety and efficacy). In such a case, those two products could not be regarded as essentially similar.⁵³

Nevertheless, the substitution of one salt for another requires – according to Community Legislation – a new marketing authorisation to be applied for.⁵⁴

This judgement is in line with the two others, as it also states that the criteria for 'essential similarity' (here the aspect of qualitative composition) are to be interpreted in a wider sense. Moreover it is clearly pointed out that the background behind the comparison of two medicinal products with respect to 'essential similarity' is the *safe-guarding of public health*, i.e. 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.

In conclusion, the EU Commission as well as the ECJ in its judgements rejects a new data protection period for line extensions. This position has been incorporated in the new legislation. The normal procedure for the marketing authorisation of such line extensions is the hybrid abridged procedure, i.e. the marketing authorisation holder of the original marketing authorisation makes reference to his own data and submits additional data to bridge the gap to the new marketing authorisation.

⁵¹ ECJ C-74/03, 'SmithKline Beecham' paragraph 40 (p. 7).

⁵² ECJ C-368/96, 'Generics', paragraph 36 (p. 12), cf. also: NtA Vol. 2a, ch. 1.

⁵³ ECJ C-74/03, 'SmithKline Beecham' paragraph 39 (p. 7).

⁵⁴ Commission Regulation EC/541/95, now substituted by Commission Regulation EC/1084/2003. The wording to which the court refers is virtually identical in the new Regulation.

2.2.2 Line Extensions and Abridged Applications of Centrally Authorised Products

Up to now, the discussion was centered around national marketing authorisations (according to Directive 2001/83/EC). Still it is a different question, whether line extensions of centrally authorised medicinal products could be attributed a new data protection period. As said above, the respective provision for the data protection period entered into force on 01.01.1995, thus the question of abridged applications for the CP is relatively new. The general aspects of abridged applications under the CP are regulated in the Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03).⁵⁵ This Commission Communication makes reference to Directive 2001/83/EC Art. 10 as regards the requirements for abridged marketing authorisation applications under the CP. For an abridged procedure the dossier of the original medicinal product must be at the disposal of the competent authority. The competent authority in the case of a CP is the EMEA, therefore the Commission Communication states that an abridged procedure (generic or line extension) related to a centrally authorised medicinal product must also use the CP. This has partly been changed with the new legislation.⁵⁶

With respect to a data protection for line extensions of centrally authorised medicinal products, the judgements of the ECJ (though related to national marketing authorisations) suggest that there will also be no new data protection for line extensions. However, some experts say that a new data protection period for line extensions of centrally authorised is possible, if *only* the name of the medicinal product is kept and no reference to old indications or pharmaceutical forms is made.⁵⁷

Prior to the discussion of the changes with the new legislation a third kind of intellectual property protection must be mentioned: the market exclusivity for Orphan Medicinal Products.

⁵⁵ Commission Communication 98/C 229/03.

⁵⁶ According to the new legislation the use of the CP is no longer required for *generic medicinal products* making reference to a centrally authorised medicinal product [Art. 3 (3) of Regulation EC/726/2004]. It is still required for *line extensions* of the original medicinal product [based on Art. 6 of Directive 2001/83 as amended, specifically Art. 1 (5) a of Directive 2004/27/EC, containing the concept of the 'global marketing authorisation'].

⁵⁷ STRÄTER, 2005. A probably more promising alternative may be a *complete new application* under a new name, with no reference being made to the old indications and pharmaceutical forms, cf. below the discussion in ch. 4 of this thesis.

2.3 Orphan Drug Regulation – Market Exclusivity

The introduction to the Regulation on Orphan Medicinal Products (Regulation EC/141/2000) names the main intention behind this Regulation: Some serious diseases are so rare that under normal market conditions a pharmaceutical company may not be willing or not be capable of investing in the development of medicinal products intended for the diagnosis, prevention or the treatment of such diseases. Therefore, the Regulation on Orphan Medicinal Products was adopted to stimulate the development of medicinal products for rare diseases and conditions. Similar provisions exist in the two other ICH regions.

According to Regulation EC/141/2000 the following conditions must be met to obtain a designation as an orphan drug: (Art. 3):

"(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition."

The abovementioned criteria for an Orphan Drug Designation (prevalence in the Community, potential for return of investment, and existence of other methods of treatment) are further elaborated in the Regulation EC/847/2000.

The application for a designation as an orphan drug may be made at any stage during the development of a medicinal product but must be made *before* the application for marketing authorisation is submitted. The application for an Orphan Drug Designation is made at the EMEA and assessed by the COMP (Committee on Orphan Medicinal Products). More than one sponsor may apply for and may obtain an Or-

phan Drug Designation; additionally, an Orphan Drug Designation may also be granted for a new indication of an already authorised medicinal product which makes this concept interesting for the development of known drug substances.⁵⁸

If granted the designation as an Orphan Medicinal Product, the applicant can benefit from various incentives. Those incentives include scientific advice by the EMEA (Protocol Assistance), reduction or complete waiving of fees payable, direct access to the centralised procedure for marketing authorisation (which otherwise is accessible only for certain classes of medicinal products, as given in the Annex of Regulation EEC/2309/93) research grants and – most important in the context of intellectual property: a 10-year period of 'market exclusivity' (if the medicinal product obtains a marketing authorisation).

This market exclusivity is different from data exclusivity as well as patent protection. As laid down in Art. 8 (1) of Regulation EC/141/2000 market exclusivity means that neither the Community nor the Member State shall:

- accept an application for a marketing authorisation
 - grant a marketing authorisation
 - accept an application for an extension of an existing marketing authorisation
- for the *same indication* for a *similar medicinal product*.

This provision hinders other applicants to rely on the data submitted for the marketing authorisation (which is equivalent to data protection) but it also provides a very effective protection against the so-called 'Me-toos' (i.e. developments with only minor changes to the active substance to circumvent the patent protection). In this respect, the granted market exclusivity can even be more effective than patent protection, as the term "similar medicinal product" is to be interpreted in a much wider sense than the term "essentially similar" discussed in the last paragraph of this thesis.

The term "similar medicinal product" is defined in Regulation EC/847/2000. According to this Regulation a similar medicinal product is a product containing a "similar active substance" which means a substance with the "same principal molecular

⁵⁸ See Regulation EC/847/2000, Art. 2 (4) (a) and (b). For example, in the EU Register of Orphan Drug Products/Designations there is mentioned the well-known acetyl salicylic acid as the active substance for an Orphan Drug application (www.pharmacos.eudra.org).

structural features (but not necessarily all of the same molecular structural features)" acting via the same mechanism as the authorised Orphan Drug product.

The substances that would be considered as similar in this respect include: other isomers, complexes, esters, salts of the original active substance, substances exhibiting only minor changes in the molecular structure in relation to the reference product, biopolymers with only minor changes to their structure (proteinaceous substances, polysaccharides, polynucleotides, other biotechnology products as e.g. viral vaccines).

This 10-year market exclusivity may be reduced to six years if in an assessment after the fifth year it turns out that the conditions of Art. 3 are no longer met [Art. 8 (2)].

Additionally, the marketing authorisation for similar medicinal product with the same indication may be granted if [Art. 8 (3)]:

- the marketing authorisation holder has given his consent
- the marketing authorisation holder cannot supply sufficient quantities of the medicinal product
- the new product is safer, more effective or otherwise clinically superior⁵⁹

After having given this overview on intellectual property and data exclusivity rights according to the legislation prior to the EU review, the next chapter will be concerned with the main changes in this field that will come into force with the new legislation.

⁵⁹ Again, the definition of clinical superiority is given in Regulation EC/847/2000.

3. Changes with the Review of EU Legislation

The Directive 2004/27/EC and the Regulation EC/726/2004 were adopted in 2004. The Regulation became binding law on the 20th day after its publication in the Official Journal of the EU. The Directive instead, needs to be transposed into the national law of the Member States for which a period until the 30.10.2005 has been given. Independently, for some provisions in the new legislation different time lines apply. First, the main changes related to intellectual property shall be discussed, than the time schedule for the data exclusivity provisions shall be given. In the last part the relevant intellectual property issues in the proposed Regulation on medicinal products for the paediatric population shall be presented.

3.1 Patent Protection

The main change with respect to patent protection coming into force with the new legislation is the introduction of the so-called Roche-Bolar-Provision (termed after a prominent court case in the USA).

Art. 10 (6) of the amended Directive 2001/83/EC [Art. 1 (8) of Directive 2004/27/EC] states that:

"Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 [those paragraphs that are related to abridged 'generic' applications, comment of the author] and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products."¹

It can be deduced from this wording, that all actions are allowed - without infringement of patent law – *that are necessarily related to process of applying for a marketing authorisation of a medicinal product,*² i.e.:

- to perform the necessary tests and trials to prove the bioequivalence of generic and reference medicinal product and to prove that there are no significant differences in respect to safety and efficacy.

¹ Directive 2004/27/EC, Art. 1 (8).

- to perform the necessary tests and trials to fill the 'gap' between the reference product and the generic medicinal product, e.g. in cases of changes to the active substance, therapeutic indications, the strength, pharmaceutical form or the route of administration.
- to perform other actions which are requirements for conducting such tests and to obtain a marketing authorisation ("consequential practical requirements"), this would include:
 - development of a manufacturing process for the active substance and upscaling of such a process for production
 - import of the active substance, in the amount needed for the preparation of batches for non-clinical tests and clinical trials³ (taking into account the provisions laid down in Title IV of 2001/83/EC as amended)
 - development of the manufacturing process for the finished product and upscaling of such a process for production
 - production of batches for stability testing, validation, and the nonclinical and clinical testing
 - manufacture and submission of samples for the competent authorities

On the other hand, it would be prohibited to perform any actions connected to the *actual marketing* of the generic medicinal product, namely the import or production of the active substance or the finished form for market launch. For the same reason, it will probably also be an infringement of patent law, if the abovementioned validation batches are later on used for market launch.

It is to be awaited, that the term "consequential practical requirements" will subject to jurisdictional clarification.

This provision of the new Directive simplifies not only the development of direct generic 'copies' of the reference medicinal products but also the development of variants with different pharmaceutical forms, different routes of administration or intended for other indications than the original. Their research and development becomes more easy relying on the abovementioned paragraph.

Art. 10 (6) will be effective in the different EU Member States as soon as it is transformed into national law. According to Art. 3 of Directive 2004/27/EC, the Member

² VIGENSCHOW, 2004.

³ STRÄTER, 2005, p. 11.

States are obliged to bring into force the respective laws and provisions in order to comply with the Directive no later than the 30.10.2005, so this important change to patent protection should also take effect after that date.

As a result, the Roche-Bolar-clause opens the market for an intensified generic competition, which is an explicit aim of the new Directive:

"Since generic medicines account for a major part of the market in medicinal products, their access to the Community market should be facilitated in the light of the experience acquired. Furthermore, the period for protection of data relating to pre-clinical tests and clinical trials should be harmonised."⁴

3.2 Data Protection

With Directive 2004/27/EC the old Art. 10 of 2001/83/EC has been given a complete new wording and has been amended with further provisions. Important issues have been the clarification of the question of generic applications and line extensions based on the judgement of the ECJ as well as precise definitions of the underlying terms. In particular, the term 'essentially similar' has been eliminated from the text and been replaced by its definition given in the ECJ-case 368/96 (and the NtA).

'Global' Marketing Authorisation

The Art. 6 of Directive 2001/83/EC contains the general requirement of a marketing authorisation for a medicinal product that is to be marketed in the Community. The first part of this Art. 6 has not been changed, it states that a medicinal product may only be placed on the market if it has been authorised either according to "this Directive" (i.e. Directive 2001/83/EC as amended) or to Regulation EEC/2309/93. After this first subparagraph Art. 6 is amended [Art. 1 (5) (a) of Directive 2004/27/EC] by introducing the new concept of a 'global' marketing authorisation:

"When a medicinal product has been granted an initial 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)⁵ (which is the Article related to abridged applications).

All further developments of an initial marketing authorisation are considered as belonging to the same marketing authorisation. And though some developments of an existing marketing authorisation are considered – under a regulatory aspect - as a *new* (extension) application (cf. above), all of these are linked to the first authorisation and thus only the first authorisation is attributed the data protection period. This wording takes up the abovementioned decisions of the ECJ and the regulatory practice of the competent authorities. So, with the new legislation there is no new data protection period for line extensions.

As the first subparagraph of Art. 6 refers not only nationally authorised products but also to those authorised according to Regulation EEC/2309/93 the rejection of data protection for line extensions is also aimed for *centrally authorised medicinal products* (Art. 88 of Regulation EC/726/2004 says that all references to Regulation EEC/2309/93 must be understood as references to Regulation EC/726/2004).

It is noteworthy that though strength, pharmaceutical form, and route of administration are mentioned therapeutic indications are not explicitly referred to. The reason for this is that in order to promote the finding of new indications for existing pharmaceuticals special incentives with respect to data exclusivity are provided in Directive 2004/27/EC. The other more formal reason is that the addition of a new indication is only a type II variation of an existing marketing authorisation. It does not require a new application (cf. chapter 2 of this thesis).

New Data Protection Period – Formula 8 + 2 + 1

The new Art. 10 of Directive 2001/83 [Art. 1 (8) of Directive 2004/27/EC] provides for the first time legal definitions of 'reference medicinal product' and 'generic medicinal product'. The definition of 'generic medicinal product' takes up the wording from the generics case and the Notice to Applicants, i.e. a generic medicinal product is characterised by the same qualitative and quantitative composition in active substances

⁴ Directive 2004/27/EC, introduction reasoning 14, L136/35

⁵ Directive 2004/27/EC, Art. 1 (5) (a).

and the same pharmaceutical form as the reference medicinal product, and by its bioequivalence with the reference product (which has to be proved by bioavailability studies). Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, as long as they show no significant differences with respect to safety and efficacy. The old 'informed consent' marketing authorisation application is shifted to a separate Art. 10c, which generally states that the marketing authorisation holder may allow use to be made of his data for the examination of subsequent applications for medicinal products having the same qualitative and quantitative composition in active substances and the same pharmaceutical form. The third criterion of 'essential similarity' (bioequivalence) is not included. The well-established use (bibliographical application) is addressed in a new Art. 10a, whose wording is virtually identical to the one used in the old version of Directive 2001/83/EC.

Based on these new definition an applicant is not required [Art. 10 (1)] to provide the results from non-clinical tests and clinical trials if his product is a generic to a reference medicinal product which is or has been authorised in a Member State or in the Community for *not less than eight years*.⁶

The placing on the market of the generic medicinal product may take place *after ten years have elapsed* since the first marketing authorisation of the reference product. This period of 10 years is *extended for another year*, if the marketing authorisation holder of the reference medicinal product *during the first eight years of data protection* obtains a marketing authorisation *for one or more new therapeutic indications* which during the evaluation are considered to bring *significant clinical benefit* compared to existing therapies [Art. 10 (1) the amended Directive 2001/83/EC]

The same data protection provisions are found in the Regulation EC/726/2004 for centrally authorised products [Art. 14 (11)]. Thus, for the first time, the data protection periods for all marketing authorisations in the EU are harmonised, though it has

⁶ Additionally, the old requirement for the original medicinal product *of being marketed in the Member State for which the generic application is made* has been eliminated. Thus, marketing of the original medicinal product for not less than eight years in a Member State opens the way to generic applications in all Member States (so-called 'Euro-Generic'). There are a number of difficulties in the practical handling of this provision.

to be said that due to the long transition period (cf. below) this harmonisation will take a long time.

The extra year for a new indication is to be seen as an incentive for originators for further developments of their products.

The following aspects need to be stressed:

- *The actual data protection period is only eight years*, in the following 2 (or 3) years only the *marketing* of the generic product is not allowed⁷ (nevertheless, for reasons of simplicity in the further discussion the author will refer to the whole 8 + 2 + 1 period as 'data protection period'), e.g. applications for generic products may be filed and granted during these 2 (or 3) years.
- In contrast to the other provision of the Directive 2004/27/EC related to indications (cf. below), the one-year extension covers the *whole product*, not only the new indication(s).
- The one-year extension is – as the 8 + 2 formula - accessible only to new medicinal products, i.e. products whose marketing authorisation application is filed after the new legislation has come into force.⁸
- Though the incentive shall promote the finding of new indications it is not aimed at perpetuating data protection, i.e. regardless if *one or more indications* are discovered, the one-year extension is given only once.
- As indicated by the wording of the new Art. 10, the one-year extension requires two steps, i.e. a first marketing authorisation for a medicinal product and then another authorisation for a second indication. This naturally precludes that the one-year extension can be granted if during the first marketing authorisation *two indications* are applied for at the same time.
- An important issue will be the clarification of the term 'significant clinical benefit',⁹ which will probably be defined in an official document of the Commission or the Council. In a consultation letter (MLX 317) released by the UK regulatory agency, the MHRA takes the view, that the indication under question "had not previously been authorised in relation to any other product containing the same active substance and/or extended to new categories of patients".¹⁰

⁷ PERRY, 2004.

⁸ MLX 317, 2005 and MLX 317 ANNEX, 2005, p. 11, cf. also below.

⁹ MAILLY, 2005.

¹⁰ MLX 317 ANNEX, 2005, p. 11/12.

The new data protection periods and the effect of the Roche-Bolar clause for the marketing authorisation of generic medicinal products are summarised in the following figure:

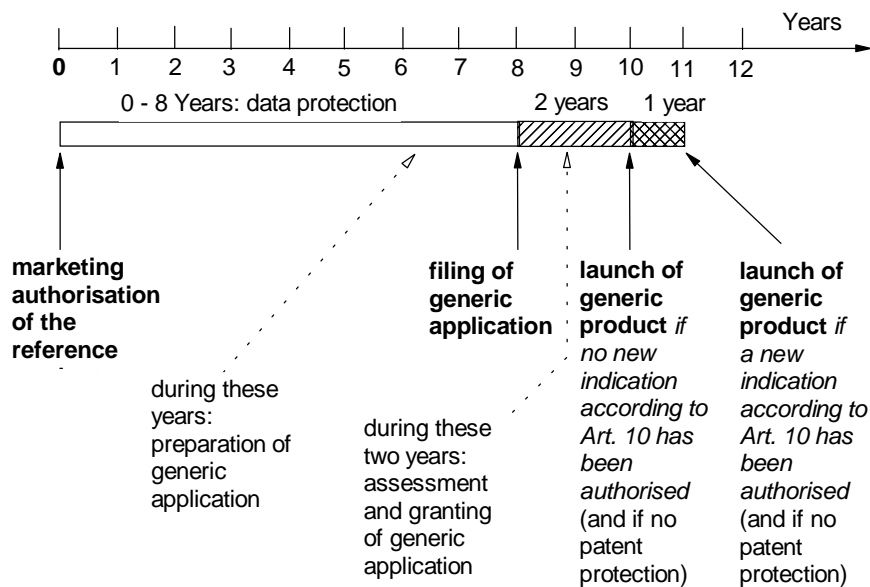


Abb. 6: Generic development under the new data protection period.

1 Year data protection for well-established use products

Art. 10 (5) of the amended Directive 2001/83/EC [Art. 1 (8) of Directive 2004/27/EC] grants a one-year data protection for the finding of a new indication for a well-established use product:

"In addition to the provisions laid down in paragraph 1, 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."¹¹

As defined in Art. 10a [or Art. 10 (5) of the old Directive 2001/83/EC] and in the Annex I to this Directive¹², well-established use refers to a use of a medicinal product within the Community for *at least 10 years*. According to the Notice to Applicants, well-established use does not simply mean authorised, but must be understood as *continuous and documented use for the indication that the medicinal product has*

¹¹ Directive 2004/27/EC, Art. 1 (8).

been authorised for. This also includes a continuous scientific interest as reflected in the scientific literature (cf. chapter 2 of this thesis).¹³

As is obvious from the fact that the medicinal product is already in long-time use (mostly, several versions based on the same active substance will exist), the granted data protection period is *limited to the data referring to the new indication* (though this is not explicitly said in the text).

The most critical issue in this paragraph is the term 'non-cumulative'. All overviews on the new legislation mention the provision for well-established use products. Unfortunately, the frequency of mentioning this provision does not correspond to an equally frequent explanation, how it is to be understood.¹⁴ On the IGPA Conference of the European Generics Medicine Association (EGA) in June 2004, Greg Perry, Director General of the EGA pointed out the ambiguity of the term 'non-cumulative' and demanded a concise definition.

Basically, there may be three meanings:

- a) 'Non-cumulative' means that the year of data protection is granted only once, so that there is no possibility to further extend this data protection by finding more new indications.
- b) 'Non-cumulative' means that it cannot be combined with any other data protection, in particular with the formula (8 + 2 +1), thus hindering a further extension of data protection to eventually 12 years.¹⁵
- c) 'Non-cumulative' applies to both cases.

There is strong evidence that 'non-cumulative' must be understood in the first sense: As mentioned above, even for new medicinal products (*if more than one* new indication is discovered) the new legislation limits the additional protection period to one year. So, it may well be concluded that this is also intended for well-established use products. Furthermore, it is helpful to know, that an additional data protection for new indications for well-established use products *was not included* in the original draft of the new Directive 2004/27/EC (published as Common Position EC No. 61/2003).¹⁶ On the contrary, an amendment (No. 40) granting a *three* year data protection period

¹² Directive 2003/63/EC, Part II, 1.

¹³ NtA Vol 2a, ch. 1.

¹⁴ Cf. e.g. GENERICS BULLETIN, 2004; PERRY, 2004; MAILLY, 2005.

¹⁵ STRÄTER, 2004; BÜTTRICH, 2004; GENERICS BULLETIN, 2004.

¹⁶ Common Position 61/2003.

for new indications for a well established substance was explicitly rejected.¹⁷ This supports the interpretation that the present wording is a compromise and that 'non-cumulative' is meant to hinder a further prolongation of the one-year data protection period.

Less convincing is the interpretation b). First the Art. 10 (5) starts by saying "*In addition to the provisions laid down in paragraph 1 ...*" (Italicisation by the author) suggesting that this provision is independent of the regulations in paragraph 1. This is also consequent in a systematic sense, as the two data exclusivity provisions are aimed at two different kinds of exclusivity: The development of a new indication referred to in Art. 10 (1) leads to an extension of data exclusivity for the *whole product*, whereas the new indication mentioned in Art. 10 (5) *relates only to the data for the new indication*.

Second, if the originator of a medicinal product (having obtained the 8 + 2 + 1 data protection period) is not allowed to refer to this paragraph, claiming this year of data protection for his well established use product, he would be denied what all other (generic) manufacturers are granted, i.e. to develop/find a new indication for an already existing medicinal product.¹⁸ So in the opinion of the author the wording of Art. 10 (5) does not preclude, that an originator may obtain this one-year data protection in addition to the 8 + 2 + 1 period provided in the amended Regulation 2001/83/EC.

In support of this interpretation, the MHRA consultation letter MLX 317 shall be quoted:

"The "non-cumulative period" is considered to mean no more than one additional year of data exclusivity can be awarded for a particular authorisation. This additional year of data exclusivity can however be awarded whether or not the original product had already benefited from an additional one year of market exclusivity under the 4th paragraph of Article 10(1)."¹⁹

In practice, it may well be that this question will not be of major importance, because, as indicated above, the simple fact that a medicinal product has been authorised for

¹⁷ Common Position 61/2003, p. 30.

¹⁸ GENERICS BULLETIN, 2004.

¹⁹ MLX 317 ANNEX, 2005, p. 14.

at least 10 years *does not qualify it* as a well-established use product, i.e. it is improbable, that an originator, directly after the maximum data protection period (11 years) has expired, can qualify his product for well-established use.

Nevertheless, the interpretation of this term will need further clarification. The same holds for the term 'significant pre-clinical or clinical studies'. This will certainly include controlled clinical trials in the target patient population, i.e. bibliographic data will not be sufficient.²⁰

Though this one-year data exclusivity for a new indication of a well-established use product is introduced with the new legislation it not probable that it is to be applied only prospectively, i.e. to products that are authorised *after* the new legislation has come into force. Instead all products that qualify for the criterion of well-established use as defined above will probably have access to this provision.²¹ Otherwise the effect of this provision would be postponed for a period of more than 10 years.

Last, it should be mentioned that though this data protection period is limited to one year for a given *medicinal product*, this does not mean, that there can not be several one-year data protection periods (for several indications) granted for the *same active substance*, where several different medicinal products - from different pharmaceutical companies - related to the same active substance exist. One issue arising in this case is the question of harmonisation, which may be lost by granting data exclusivity (cf. below).

Though it is not explicitly mentioned in the Regulation EC/726/2004 the possibility for obtaining a one-year data protection period for a new indication of a well-established use product should also be possible for centrally authorised products as Art. 6 of Regulation EC/726/2004 refers to Art. 10 and Art. 10a (well-established use medicinal product) for the particulars and documents needed for marketing authorisation.

1 Year data protection for R_x - OTC-Switch

Art. 74a of the amended Directive 2001/83/EC [Art. 1 (54) of Directive 2004/27/EC] grants a one-year data protection period for those data, related to the classification

²⁰ MLX 317 ANNEX, 2005, p. 14.

²¹ MLX 317 ANNEX, 2005, p. 14. Thus in the light of the above the question arises whether this one-year data protection can also be combined with current data exclusivity periods.

change of a medicinal product from prescription only (R_x) to non-prescription (OTC, over the counter), as defined in Art. 71 und 72 of the amended Directive 2004/27/EC: "Where a change of classification of a medicinal product has been authorised on the basis of significant pre-clinical tests or clinical trials, the competent authority shall not refer to the results of those tests or trials when examining an application by another applicant for or holder of marketing authorisation for a change of classification of the same substance for one year after the initial change was authorised."²²

This possibility of a one-year data protection for an R_x-OTC-Switch does also exist for centrally authorised products, for which a change from R_x to OTC is approved after 20.11.2005.²³ The legal status for OTC products in the Centralised Procedure is the same as for nationally approved medicinal products as the criteria given in Directive 2001/83/EC as amended apply.

Though introduced with the new legislation, this provision will certainly be available to all medicinal products once it has come into force in the Member States.²⁴

A special problem of this provision is that the classification of a medicinal product (as R_x or OTC) is usually subject to national regulation, so problems will arise, if during a Mutual Recognition Procedure (MRP) or a Decentralised Procedure (DP), different positions are taken by the EU Member States involved.

Evaluation of "significance" during MRP, DP and CP

This points out to a general prospective difficulty with the new data protection provisions. All of them include a wording prone to evoke different interpretations that may lead to vivid discussions among the Member States during an MRP or DP:

"... considered to bring significant clinical benefit ...": prerequisite for granting the one-year data protection in addition to the 8 + 2 data protection period, Art. 10 (1).

"... provided that significant pre-clinical or clinical studies were carried out ...": prerequisite for granting the one-year data protection for a new indication of well-established use products, Art. 10 (5).

²² Directive 2004/27/EC, Art. 1 (54).

²³ LE COURTOIS, 2005.

²⁴ The UK has already introduced this provision as of January 2005, cf. MLX 309, 2004 and MLX 309 OUTCOME, 2004.

"... has been authorised on the basis of significant pre-clinical tests or clinical trials ...": prerequisite for the abovementioned data protection for the R_x - OTC-Switch, Art. 74a.

Moreover, the question of data protection is (via the suspension of generic competition or the different reimbursement provisions for R_x/OTC medicinal products) closely related to the costs for the different national health systems of the Member States, thus, in the question of whether or not a data protection period is granted, the positions of the Member States may well be different, apart from the general difficulty to determine the required 'significance' of clinical trials scientifically.

At present, it is not completely clear, how problems arising from different positions of the Member States during the MRP or DP with respect to these evaluations for granting data protection shall be resolved.

The abovementioned consultation letter of the MHRA cross-references the EU interpretation with respect to "significant clinical benefit" [Art. 1 (8) of Directive 2004/27/EC] by saying that this question will be evaluated in the assessment report and discussed when this report is shared with the other Member States during MRP, DP or the CP.²⁵ But what, if no agreement is reached during these discussions?

The 'normal' procedure for resolving problems associated with the mutual recognition of marketing authorisations is the arbitration procedure described in Art. 32, 33 and 34 of Directive 2001/83EC as amended. This arbitration procedure may be invoked based on i) inability of the Member States to reach agreement during the MRP or CP [Art. 29], ii) divergent decisions of the Member States concerning a medicinal product [Art. 30], iii) in cases of Community interest [Art. 31], and iv) to maintain an achieved harmonisation of a marketing authorisation for a medicinal product, the so-called 'Follow-up referral' [Art. 35, 36, and 37]. The problem is that the main trigger for those arbitration procedures is a concern about public health, i.e. they are not intended to solve problems with divergent decisions related to intellectual property. And though the protection of public health is naturally the basis for granting the marketing authorisation for a new indication for a medicinal product, the question of whether the studies and trials provided by the applicant satisfy the criterion of being

'significant' insofar as to justify additional data protection is certainly not directly connected to a concern about public health. In consulting the Notice to Applicants there is one reason for an arbitration that may serve as a basis in cases of divergent opinions of the Member States on the granting of data exclusivity for new indications: With respect to the *Community Interest Referral*, the NtA say that:

"This referral may be started in specific cases where the interests of the Community are involved. *The expression "interest of the Community" has a very broad meaning.* It refers particularly to the interests of the Community public health related to a medicinal product which is on the market in the European Union in the light of new data related to quality, safety and efficacy or new pharmacovigilance information *but is not limited to this case.* The interests of the Community are set out in the EC Treaty and cover – amongst others – *the creation of an internal market*, the attainment of a high level of health protection, strengthening of consumer protection, *avoidance of distortion of competition* and environmental protection"²⁶ (Italicisation by the author)

So, perhaps this referral procedure could serve as a tool to maintain harmonisation. It may also be that an alternative to a formal arbitration procedure is found, e.g. based on the coordination group which was introduced with the new Directive 2004/27/EC [Art. 27] ("A coordination group shall be set up for the examination of any question relating to marketing authorisation of a medicinal product ..."), and by which the mutual recognition facilitation group (MRFG) has been given an official status in the marketing authorisation procedure. This will be easier, as there is still a long period, until the data protection periods of new Regulation and the new Directive will take effect. This will be the subject of the next paragraph.

3.3 Time Schedule for Coming into Force of the New Data Protection Provisions

The time schedule given in Regulation EC/726/2004 and Directive 2004/27/EC will cause an extremely long transition period, during which both, old and new data protection periods will co-exist. This poses quite a challenge to the regulators in the pharmaceutical industry, especially the generic industry. The main principle underlying

²⁵ MLX 317 ANNEX, 2005, p. 11.

ing the time schedule for the new legislation is that the new data protection periods are effective only for those medicinal products for which an application for marketing authorisation is filed *after* the dates given in the legislative texts.

3.3.1 Nationally Authorised Medicinal Products (Single Member State, MRP, and DP)

Art. 3 of Directive 2004/27/EC states that "Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive no later than 30 October 2005." And Art. 2 says that "The periods of protection provided for in Article 1, point 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 first paragraph."²⁷

Thus, if the application for a marketing authorisation of a medicinal product *is filed prior* to the date at which the national legislation (which transposes Directive 2004/27/EC into national law) is coming into force, then the old data protection periods apply (6 and 10 years, respectively). The new data protection period (8 + 2 + 1) are therefore valid for every application for marketing authorisation *filed after* the national legislation has come into force, i.e. after the 30.10.2005 at the latest (if the Member States comply with above regulation!). So, in 2005, the *filing date* for an application for marketing authorisation of a medicinal product determines the data protection period.

This is again visualised in the following diagram:

²⁶ NtA Vol 2a, ch. 3 (Community Referral).

²⁷ Directive 2004/27/EC, Art. 2 and 3.

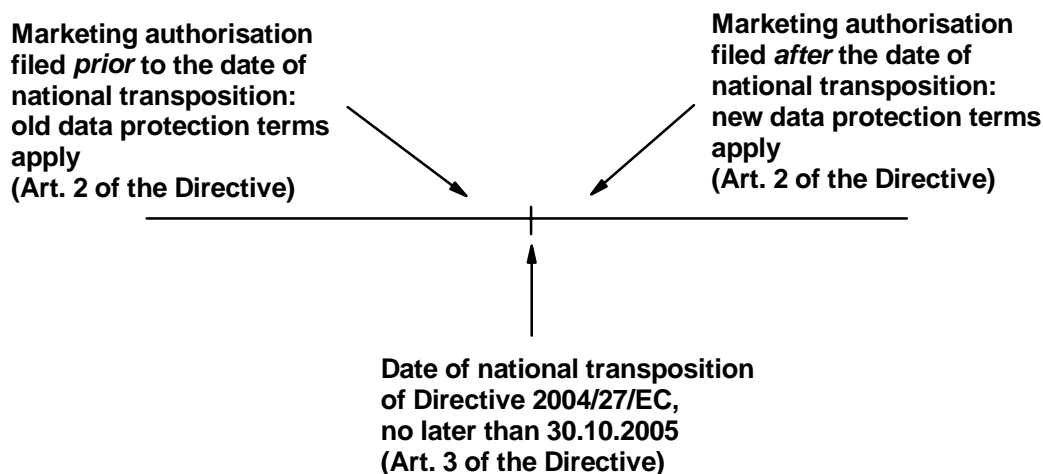


Abb. 7: Validity of 'old' and 'new' data protection periods.

According to this time schedule, the first generic applications, making reference to medicinal products authorised with the new data protection period, may be filed in 2013 (or 2012, if the legislation was already adopted in a Member State in 2004), i.e. 2005 plus 8 years.²⁸

But, the prerequisite is that all Member States comply with the new Directive, which is not sure, as several new EU Member States have requested derogations from the new data exclusivity provisions, e.g. Poland has requested a 15-year transition period.²⁹

All other provisions of Directive 2004/27/EC are valid as soon as the transposition into national law has taken place, e.g. in Germany with the adoption of the 14th AMG amendment. This concerns e.g. the possibility of one-year data protection for a new indication for a well-established use medicinal product, the potential one-year data protection for an R_x -> OTC-switch, or actions falling under the Roche-Bolar-clause. There may even be differences for single provisions. For example, the UK has already introduced the one-year data protection for R_x-OTC-switch as of January 2005, though the other data exclusivity provisions will come into force as indicated by the Directive.

²⁸ IDRAC 'EU Review', 2005; MAILLY, 2005.

²⁹ MAILLY, 2005

3.3.2 Centrally Authorised Medicinal Products

As said above, the Regulation EC/726/2004 establishes the same data protection formula (8 + 2 + 1) as Directive 2004/27/EC, i.e. 8 years of data protection, marketing is not allowed for 10 years, an additional year of market protection is given for a new indication with significant clinical benefit. With respect to the date of coming into force, the Regulation also tries to establish a harmonisation with the Directive. Art. 90 says that:

"This Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

By way of derogation from the first paragraph, Titles I, II, III and V shall apply from 20 November 2005 ..."³⁰

And Art. 89 states: "The periods of protection provided for in Articles 14(11) and 39(10) shall not apply to reference medicinal products for which an application for authorisation has been submitted before the date referred to in Article 90, second paragraph."³¹

So, if the application for a Community marketing authorisation is filed before the 20.11.2005 the old data protection provision is valid (10 years of data protection, no extension for a new indication). If the application for a central marketing authorisation is filed as of the 20.11.2005, the new data protection formula (8 + 2 + 1) applies. Here again, simply the filing date in 2005 determines the relevant data protection provisions, making the filing date a strategic question for the regulatory affairs management.

3.4 Incentives in the Proposal for a Regulation for Paediatric Medicinal Products

The pharmaceutical legislation is - apart from its basic purpose to safeguard public health – also a tool to guide pharmaceutical research and to promote pharmaceutical development in specific directions. There are situations where obviously the market forces alone are insufficient to guarantee an adequate supply of treatments for cer-

³⁰ Regulation EC/726/2004, Art. 90.

tain patient groups. One prominent example is the Orphan Drug Regulation which has successfully contributed to the finding of treatments for rare diseases. Another field where there is a strong lack of suitably authorised medicinal products are medicines for paediatric use. It has been shown that currently less than 50% of the medicines used to treat the children in Europe have been tested for use in children and are authorised for use in children.³² In many cases medicinal products are prescribed "off-label" with the risk of ineffectiveness or adverse reactions. The USA have introduced two complementary pieces of legislation, the 'Paediatric Rule' and the 'Paediatric Exclusivity' (in 1998 and 1997, respectively), to intensify the development of medicines for children. Together with follow-up regulations (as the 'Best Pharmaceuticals for Children Act' in 2002) these measures have been very successful in stimulating paediatric research and authorisation of medicinal products for children.³³ On the 29.09.2004 the European Commission presented the official draft of a new Regulation on medicinal products for paediatric use.³⁴ The earliest date for this Regulation to come into force is the fall of 2006. Though this draft will undergo further changes in the process of legislation, it will contain important provisions for data exclusivity – as these are the main incentives used to promote research – and thus, the main points with respect to data exclusivity rights shall be shortly discussed here.

As in the US, there will be a combination of the necessity to acquire data in respect to a paediatric use and incentives to do so.³⁵

A Paediatric Committee will be established having expertise in all aspects related to medicines for children. All studies in children will be conducted according to a 'Paediatric Investigation Plan' (PIP) which has been agreed with the Paediatric Committee.³⁶ When assessing the PIP the Paediatric Committee will be guided by two main principles:

- clinical studies should only be performed, where a potential therapeutic benefit for children is to be expected.

³¹ Regulation EC/726/2004, Art. 89.

³² PAEDIATRIC PROPOSAL, 2004, p. 2; PAEDIATRIC PROPOSAL FAQ, 2004, p. 5.

³³ PAEDIATRIC PROPOSAL FAQ, 2004, p. 7, as of February 2004, 63 new paediatric labels were introduced and 661 studies requested,

³⁴ PAEDIATRIC PROPOSAL, 2004.

³⁵ In some publications this is referred to as the 'ball and stick' combination.

³⁶ PAEDIATRIC PROPOSAL, 2004, Art. 16.

- the requirement of studies in the paediatric population shall not delay an authorisation of a medicinal product for other populations.

The PIP is to be presented at the time of application unless a waiver or a deferral has been granted. Waivers are meant for cases, where there is no potential benefit for children, e.g. medicinal products for diseases which do not occur in the paediatric population. Deferrals are granted if e.g. further experience on the use of the medicinal product in adults is necessary before a use for the paediatric population may be feasible.

The fulfilment of the PIP agreed with the Paediatric Committee is also the central issue with respect to the data exclusivity provisions.

Art. 8 of the proposal requires that for new medicinal products (which includes line extensions of existing medicinal products) to be authorised according to Art. 6 of Directive 2001/83 as amended all results and informations from studies according to an agreed PIP have to be provided, unless a waiver or a deferral has been granted. Applicants for a marketing authorisation for paediatric indication(s) may - based on an agreed PIP - also choose the centralised procedure (Art. 29).

For older existing medicinal products, incentives to acquire information according to a PIP are presented.

With respect to the incentives, three groups of medicinal products are divided:

Medicinal products protected by patent or SPC: 6 month extension of the SPC

According to Art. 36 of the proposal, all products that are protected by an SPC or by a patent that qualifies for the granting of an SPC shall be rewarded a six-month extension of the SPC if studies to an agreed PIP have been completed. Of course, this applies also to the abovementioned new medicinal products. A prerequisite is, that the medicinal product is authorised in all Member States.³⁷ It is important to notice, that this 6 month extension of patent protection of the active moiety is granted even if the studies according to the PIP *do not lead to the authorisation of a paediatric indication* but are reflected in the summary of product characteristics. Orphan medicinal products are exempted from this incentive.

Orphan medicinal products: 2 years extension of market exclusivity

For Orphan medicinal products, Art. 37 of the proposal grants a 2-year extension of the market exclusivity to these products as described in Regulation 141/2000/EC, i.e. twelve years of market exclusivity altogether. Again, this additional market exclusivity is granted even in the case of 'negative' results from the completed PIP. This market exclusivity provision for Orphan medicinal products is especially important because at present about 40-50% of the Orphan Drug Designations are designations for paediatric indications.

Medicinal products *not* protected by patent or SPC: PUMA

The third group of medicinal products are those that are no longer protected by patent or SPC, a group which covers off-patent medicinal products from originators, as well as their line extensions and generic counterparts.

To create an incentive for research in the paediatric population for those products a new kind of marketing authorisation, also based on a PIP, is proposed, the paediatric use marketing authorisation (PUMA). According to Art. 31 (1) a PUMA is "... a marketing authorisation granted in respect of a medicinal product for human use [...] covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product."³⁸

The PUMA is therefore restricted to the paediatric indication, though the applicant can of course additionally apply for a marketing authorisation for other (non-paediatric) indications as expressed in Art. 31 (2).

In Art. 38 of the proposal, the PUMA is granted the same data and marketing protection periods as provided in Regulation EC/726/2004 or Directive 2001/83/EC as amended, depending on which legislative text has been the basis for the marketing authorisation, i.e. the full 8 + 2 period will apply.

³⁷ The reason behind this is, that an EU-wide effective incentive shall only be given, where children in *all* EU Member States will benefit from the medicinal product, cf. the introduction to the PAEDIATRIC PROPOSAL, 2004, p. 6.

³⁸ PAEDIATRIC PROPOSAL, 2004, Art. 31.

This ruling for off-patent medicinal products forms a strong incentive, as it is - if the proposal is accepted with this wording - an attractive possibility to obtain data protection for long-existing medicinal products (for the paediatric indication!). It refers to typical line extensions (a different strength, pharmaceutical form or route of administration, see above), which is to be seen in the context of the target patient population, where e.g. even a 'simple' change of the route of administration may constitute a significant improvement³⁹

In the explanatory introduction to the proposal the data protection associated with the PUMA is explicitly valued as an option in the light of the recent case-law of the ECJ, i.e. the refusal of data protection for line extensions.⁴⁰ Moreover this incentive is also meant to promote the development of off-patent medicines for children by generics companies.⁴¹ This is in line with the regulation that where a medicinal product is or has been authorised in the Community or a Member State its data may be referred to in an application for a PUMA [Art. 31 (4)].

Under marketing aspects, it is important that the PUMA product may retain the name of the original medicinal product [Art. 31 (5)]. As an identification mark for the paediatric use it is recommended that any product obtaining a paediatric marketing authorisation following a PIP is identified by a "P" in blue lettering surrounded by a blue star (Art. 33).

After having given this overview on the main changes with respect to data protection under the new legislation, the following concluding chapter shall discuss the options of originators to protect their developments in this legislative framework.

³⁹ As the author of this thesis has experienced during the diverse illnesses of his own children.

⁴⁰ PAEDIATRIC PROPOSAL, 2004, p. 6; PAEDIATRIC PROPOSAL FAQ, 2004, p. 12; referring to the ECJ C-106/01 'Novartis'.

⁴¹ PAEDIATRIC PROPOSAL FAQ, 2004.

4. Conclusion: Impact on Regulatory Strategies for Known Drug Substances

The new Regulation EC/726/2004 and the new Directive 2004/27/EC that will become effective in the end of 2005 have - as outlined in the previous chapter - introduced a number of decisive new provisions with respect to intellectual property and data exclusivity. Some of these new provisions take up the tenor of earlier judgements of the ECJ on data protection for medicinal products. Additional changes with respect to data exclusivity will be included in the forthcoming Regulation on medicinal products for paediatric indications (approximately in 2006). This chapter will briefly describe some possible regulatory strategies for the protection of the pharmaceutical development of known drug substances in the framework of this legislation.

The basis for the following considerations is the fact that data protection for such developments has become difficult: The new legislation, by introducing the concept of a global marketing authorisation [Art. 6 (1) of Directive 2001/83/EC as amended], is based on the view that the data protection period is given only once, starting with the first marketing authorisation of a line of products in a EU Member State or the Community. Moreover, the ECJ has issued a series of judgements pointing in the same direction (ECJ cases C-368/96, C-106/01, C-36/03, and C-74/03), thus this principle also applies for applications made under the current legislation.

First of all, the primary option for protecting step-innovations with respect to a given medicinal product is the patent. The catalogue of properties eligible to patenting has increased in recent years, e.g. new formulations, methods of administration, and dosing schemes can be protected by patents. One present prominent example is the medicinal product Yasmin (Schering AG). Though the active substance has long run out of patent protection other related patents (i.a. referring to the manufacturing process) guarantee market exclusivity making it the second top-selling product of the company.¹

There are two limitations to this: First, there may be no possibility to protect the development by additional patents, second - as is happening to abovementioned medicinal product in the US - the patent may of course be challenged by other competi-

¹ Berliner Zeitung, 31.03.05.

tive companies. This underlines the importance of data protection as an additional option.

A second point of major importance is the time schedule for coming into force of the new data exclusivity provisions: The (8 + 2 + 1)-year data exclusivity for nationally authorised medicinal products will only apply to those medicinal products whose application for marketing authorisation is submitted *after* the transposition of Directive 2004/27/EC into the national law of the Member States (i.e. as of 30.10.2005 at the latest, if there are no derogations for certain Member States). For centrally authorised products, the (8 + 2 + 1)-year data exclusivity will be valid only for applications for marketing authorisation that are submitted from the 20.11.2005. For all applications for marketing authorisation submitted *prior* to these dates the old data exclusivity periods apply (i.e. 6 or 10 years for nationally authorised products, 10 years for centrally authorised products). So, the first marketing of generic medicinal products based on the new data exclusivity periods is to be awaited as late as 2015. This also means that any discussion about combining the (8 + 2 + 1)-year data exclusivity period with other incentives, such as those mentioned in the proposal for a Regulation for medicinal products for paediatric indications is dealing with a very distant time horizon.

Consequently, more interesting is the question what options there are for medicinal products that draw benefit from the current data exclusivity periods and whose patent or data protection is expiring in the nearer future. For them, the new legislation is nevertheless important as the other data exclusivity provisions in Directive 2004/27/EC will most probably not be applied only prospectively, i.e. to products that will be authorised after the two cut-off dates mentioned above, but also to products that are currently authorised.

If not explicitly mentioned otherwise, the options discussed below refer to both, i.e. products benefiting from the old or from the new data protection periods.

The central issue in relation to data protection in the further development of known drug substances *are studies aimed at finding new indications*. Under the new legislation (cf. chapter 2) nearly all data protection provisions are connected with the finding of new indications with respect to diseases or patient groups. The only provision *not linked to the finding of a new indication* is the 1-year data protection granted for an

R_x - OTC-Switch if it is based on the results of significant pre-clinical or clinical studies (Art. 74a of Directive 2001/83/EC as amended). This option - which may be used by generic manufacturers as well as originators - is applicable to medicinal products whether still under patent or data protection or not, but is of course especially interesting for products that have no further intellectual property protection. The protection is limited to the data for the R_x - OTC-Switch, there is no protection for the product as a whole.

Based on studies for new indications, there are three options where the data protection covers the *whole product*.

The first one is the possibility to extend the (8 + 2)-year data protection period granted under the new legislation to eleven years, if during the first eight years one or more new indications are found, which bring significant clinical benefit to the patients compared to existing therapies [Art. 10 (1) of Directive 2001/83/EC as amended and Art. 14 (11) of Regulation 726/2004]. This extra year, where the marketing of a generic medicinal product is still not possible, is an incentive open only to those medicinal products whose marketing authorisation application is submitted after the two cut-off dates mentioned above.

The second possibility is part of the proposal for a Regulation on medicinal products for children: If studies according to an agreed Paediatric Investigation Plan have been completed, the medicinal product is granted a six month extension of the SPC. This extension is connected to the *performance* of studies according to the PIP, it is *not required* that these studies do actually lead to a marketing authorisation for a paediatric indication. Thus, performing studies aimed at a *paediatric indication* according to an agreed PIP leads to extension of market exclusivity in the *adult market*.

The third one is related to Orphan drugs and also part of the abovementioned proposal for paediatrics: Where studies for a paediatric indication are undertaken according to an agreed PIP for an Orphan medicinal product, the market exclusivity granted for these products according to Regulation 141/2000/EC is extended by another 2 years.² Again, the conduction of PIP-based studies, not a 'positive' result in the meaning of an actual marketing authorisation for a paediatric indication is the prerequisite for granting this extension.

The three variants mentioned above are based on an already existing protection that is extended for an additional period. But what options do exist, if there is no patent (or SPC) protection and also no data protection any more?

In the order of increasing 'size' of the data protection available, the following options can be discussed:

R_x-OTC-Switch (1 year data exclusivity): As mentioned above there is the possibility to achieve a one-year data protection for data from pre-clinical or clinical studies related to a switch from prescription to non-prescription (Art. 74a of Directive 2001/83/EC as amended). Though introduced with the new legislation this option is also accessible to products already authorised once the transposition into national law has taken place.³ The key question for this is, whether the studies performed satisfy the criterion of being 'significant' during the evaluation process by the competent authorities. Moreover during an MRP or DP, the involved Member States may take different positions with respect to this question, which bears the risk of an arbitration procedure.

New indication for a well-established use product (1 year data exclusivity): Products for which there is no patent or data protection will often qualify for the well-established use criterion, i.e. continuous and documented use for at least ten years in the Community for the indication for which the medicinal product was authorised. The development of a new indication for such products, if based on "significant pre-clinical or clinical studies" is granted a one-year data protection *for the data related to the new indication* [Art. 10 (5) of Directive 2001/83 as amended]. This option will most probably also apply to products already authorised. Again, the critical issue is to prove the 'significance' of the conducted trials during the evaluation process. One probable interpretation is that this means controlled clinical trials in the target population. There is strong evidence⁴ that the 'non-cumulative' limitation mentioned in Art. 10 (5) shall *not* mean, that it cannot be combined with other data-exclusivity provisions. Thus, there is the theoretical possibility that a medicinal product whose data protection (regardless whether old or new data protection periods) has just expired may obtain another year of protection for the data related to the new indication. In practice, though, this will prove difficult as well-established use means significantly

² It has to be stressed that this Regulation for paediatric medicinal products is still a *proposal*, which may undergo significant changes in the process of legislation!

³ In the UK, this provision was already introduced in January 2005; cf. MLX 309 OUTCOME, 2004.

⁴ Cf. above the discussion in chapter 2.

more than just 'authorised for 10 years'. How broad this provision is to be applied will also depend on its use by the pharmaceutical industry.

Orphan medicinal product (10 years market exclusivity): There are many examples, where a known drug substance has been developed for an Orphan drug indication. This is always an option for the further development of medicinal products. The marketing authorisation as an Orphan drug is related to strong incentives, namely the 10 years of market exclusivity combined with the efficient protection against competitors with 'similar medicinal products'. On the other hand under marketing aspects, it is the development of a new medicinal product, i.e. there may be made no reference to the old indications and it cannot be used for the exploitation of an existing brand name.

Paediatric Use Marketing Authorisation, PUMA (8 + 2 years data exclusivity): Much more attractive in this respect is the option outlined in the proposal for a Regulation on medicinal products for paediatric indications. If a marketing authorisation for a paediatric indication is obtained based on studies according to an agreed PIP this marketing authorisation is given the full data protection period for a new medicinal product as described in Directive 2001/83/EC as amended and Regulation EC/726/2004, respectively. This is the only provision which explicitly grants data protection to medicinal products that are typical line extensions of existing products (variations of strength, pharmaceutical form and route of administration), if intended for a paediatric indication. Notwithstanding, the applicant can in parallel pursue the marketing authorisation for other indications or patient groups. Moreover, the applicant can use the original name of the medicinal product (amended by a P and a Star in blue). That is, all variants of the medicinal product are still marketed under the same brand name.

Stand-alone Application (8 + 2 years data exclusivity): Under a regulatory aspect this last option is the most challenging one but also the one with the least chance of success. The new legislation as well as the current judgments of the ECJ are based on the concept of a global marketing authorisation encompassing the original marketing authorisation as well as any line extensions [Art. 6 (1) of Directive 2001/83/EC as amended]. But they do - in principle - not preclude the submission of an independent new application. Based on figure 3 of the present thesis the question may be put as: *What qualifies a medicinal product as an independent new medicinal product compared to variation or an extension application?* The first prerequisite is

that the application for marketing authorisation contains all relevant data as described in Art. 8 (referring to Annex I of Directive 2001/83/EC as amended).⁵ That is the application cannot make reference to data of an existing marketing authorisation as in the procedures named in Art. 10 and 10c, thus it can no longer be an abridged application. Also, the reference to already approved indications would be difficult. In this context it is worth noticing that in the abovementioned court cases C 106/01 and C 36/03 the line extensions of the originator companies were both authorised under the abridged procedure and not as independent applications. But such a new application may well use data from existing marketing authorisations at the disposal of the applicant (which also includes bibliographic data). Apart from this formal difference there is the question of the difference in content. This question takes up the definition of 'essential similarity' given by the ECJ that has been incorporated in the new legislation: Two medicinal products are 'essentially similar' if they have the same qualitative and quantitative composition in terms of the active substance, if they have the same pharmaceutical form and if they are bioequivalent unless they differ significantly with respect to safety and/or efficacy. Thus, in the case of a known active substance a new medicinal product would be required to differ in the other properties, i.e. pharmaceutical form and bioequivalence. *And, most important, it is required that the new medicinal product differs from already existing medicinal products containing the same active substance with respect to safety and efficacy.* Art. 10 of Directive 2001/83/EC as amended additionally states that the "... various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form" suggesting that a pharmaceutical form with a new release profile constitutes a relevant difference.

Based on these remarks the following scenario for a new authorisation of a known drug substance can be pictured:

- It has a complete data basis composed of existing data supported by new pre-clinical and clinical studies (i.e. not only 'bridging' data, but all relevant data are included in the marketing authorisation application).
- It has a new pharmaceutical form with a different release profile, constituting a significant difference with respect to efficacy and/or safety. This difference primarily justifies the application as a new medicinal product: due to its different properties it is -

⁵ See also NtA Vol. 2a, ch. 1.

for public health reasons – no longer a 'variation' or 'extension' of the original product (cf. ECJ C-74/03, cf. also the variation Regulations).⁶ According to the wording of the Annex II of the variation Regulations EC/1084/2003 and EC/1085/2003, an application for a medicinal product can be treated as an extension application as long as the efficacy/safety characteristics are not significantly different, suggesting that such a significant difference in the efficacy/safety characteristics 'shifts' the application from an extension application to a new application. The new medicinal product is also no longer bioequivalent, showing a different bioavailability (cf. ECJ C-106/01, stressing the bioequivalence as a prerequisite for essential similarity).

- In this different pharmaceutical form it is suitable for a new indication. The application is made only for the new indication with no reference to approved older indications.

- The product is given a new brand name.

A possible example where such a scenario may be applicable are (known) cytostatic compounds incorporated into specific new carrier vehicles such as protein nanoparticles, which show a significantly altered release profile and/or accumulation behaviour.

This fictive example hints to another question: The changes needed for an extension of medicinal product in order to qualify it potentially for a stand-alone application are such that the CP may be an option or even compulsory. It is not yet clear, under which circumstances a medicinal product with a known active substance can qualify for the CP. An application for a CP marketing authorisation will in this case probably have to be based on Art. 3 (2)b of Regulation EC/726/2004 (significant therapeutic, scientific or technical innovation). Nevertheless, the CP may be an interesting option as in this case, the question of whether or not a further development of a medicinal product is attributed a new data protection period is less clear than for nationally authorised products (i.e. it is not definitely rejected).⁷

Naturally, the larger the difference between the approved and the new medicinal product is, the larger will be the necessity to acquire additional information by (expensive) clinical and non-clinical studies. Therefore considering the enormous effort

⁶ ECJ C-74/03, 'SmithKline Beecham', paragraph 39 (p. 7).

⁷ At a DGRA workshop reference was made to comments by members of the Commission suggesting this.

which would be required to pursue this path and the chances for success this option bears a significant risk. It is more probable that this possibility can evolve as an alternative during the development of a medicinal product for a new indication.

How difficult it will be to obtain a new marketing authorisation (granted the full data protection) for a known drug substance can be seen from the following:

In the Annex of the MHRA consultation letter for implementation of the new legislation in the UK it is mentioned that the question of whether the submission of a new full dossier combined with a new brand name (or new combination products) would be included in the global marketing authorisation was already discussed in the EU during the process of legislation. Referring to the implementation of Art. 6 (1) in the UK the consultation letter states (Italicisation by the author):

"The scope of changes considered to fall within the initial MA will be as described in the amending Directive and *will encompass all versions of the original product having the same active substance(s) authorised to the same company, group of companies or their licensees. The data content of the dossier associated with such versions or their designation as extension applications will not be factors* in determining whether these form part of the same initial authorisation for purposes of applying Article 10(1)."⁸

Having briefly discussed possible options to protect the results from the pharmaceutical development of known drug substances it should be pointed out that in practice during the life cycle of a given medicinal product several of these options may be used. The additional information about a medicinal product that becomes available based on the experience from continuous use after the first marketing authorisation or from advanced research will promote the development of this medicinal product for other indications, including those for rare diseases or paediatric indications. Or the acquired information may justify to apply for its use for self-medication.

A last aspect to be mentioned is that the new legislation may further diminish the 'gap' between generic and originator pharmaceutical companies, as some of the provisions mentioned here can well be used by generic pharmaceutical companies to develop off-patent medicinal products.

⁸ MLX 317 ANNEX, 2005, p. 8.

5. Summary

In April 2004 the EU adopted the Directive 2004/27/EC and the Regulation EC/726/2004. These two pieces of legislation amended and replaced the two basic texts of pharmaceutical legislation for medicinal products for human use, respectively, the Directive 2001/83/EC and the Regulation EEC/2309/93. Thus, the 'Review 2004' has created the new regulatory environment that will be the basis for the marketing authorisation of human medicines in Europe for at least the next decade. The new legislation encompasses provisions related to all aspects of medicinal products for human use, among these are decisive changes with respect to intellectual property. The present master thesis analyses these changes in comparison with the current legislation that will still be in force until the end of 2005. An overview on the present intellectual property regulations is given, with the focus on data exclusivity provisions. Apart from patent protection which is the basic tool to protect innovations data protection can be regarded as the 'second pillar' for this purpose. Data protection becomes especially important in case of long development times and for the protection of innovations related to medicinal products that are already on the market for a considerable period. After mentioning the basic data protection provisions (6/10 years for nationally authorised products and 10 years for centrally authorised products) the specific question of abridged generic applications under the current legislation is discussed, addressing the issue of data protection for line extensions. Those further developments of known drug substances form an important part of the life-cycle of a medicinal product. The ECJ has issued a series of judgements related to this question (C-368/96, C-106/01, C-36/03, and C-74/03) in which a data protection for line extensions of an original medicinal product is rejected. The last part of this overview on the intellectual property provisions mentions the specifics of the market exclusivity granted for Orphan Drugs.

In the second part of the thesis the main provisions related to intellectual property in the new Directive and the new Regulation are summarised. The most important change with respect to patent protection is the introduction of a Roche-Bolar-like clause which significantly facilitates the development of generic medicinal products, which is one of the aims of the new legislation. For data protection, a new 'formula' is introduced (for centrally and nationally authorised medicinal products), the (8 + 2 +

1)-provision, i.e. 8 years of data protection followed by two years of prohibition to market the generic medicinal product, a period that can be extended for another year, if a new indication with significant clinical benefit is developed. Two further data protection incentives are part of Directive 2004/27/EC: a one-year data protection for data on a new indication for a well-established use product and a one-year data protection for the data on a switch from R_x to OTC, both are subject to additional restrictions.

The rejection of a data protection for line extensions of an original medicinal product as expressed by the ECJ has been incorporated in Directive 2004/27/EC with the concept of a 'global' marketing authorisation. The time lines as of which the new regulations apply are given.

In addition, the proposal for a Regulation on medicinal products for the paediatric population (presented by the European Commission in 2004) is mentioned because it will contain important provisions related to intellectual property protection that serve as a strong incentives for the pharmaceutical industry, i.a. here even a data protection for line extensions of existing medicinal product is proposed if they are intended for the paediatric population.

The last part of the thesis briefly discusses possible options for the data protection for the development of known drug substances in this new regulatory environment. It is stressed that the finding of new indications plays an important role for the regulatory strategy, as most extensions of data and market exclusivity under the new legislation are related to new indications or specific patient groups.

6. References

a) EU-Legislative and Other Official Documents

Directive 2001/82/EC: Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1 - 66).

Directive 2001/83/EC: Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Official Journal L 311, 28/11/2001 p. 67 - 128). [German and English Version]

Consolidated Directive 2001/83/EC: Consolidated Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use as amended by Directive 2002/98/EC, Directive 2004/24/EC and Directive 2004/27/EC. [English Version]

Directive 2003/63/EC: Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Official Journal L 159, 27/6/2003 p. 46 - 94). [English Version]

Directive 2004/24/EC: Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal L 136, 30/4/2004, p. 85 - 90). [German and English Version]

Directive 2004/27/EC: Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal L 136, 30/4/2004 p. 34 - 57). [German and English Version]

Directive 2004/28/EC: Directive 2004/28/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/82/EC on the Community code relating to veterinary medicinal products (Official Journal L 136, 30/4/2004 p. 58 - 84).

Regulation EEC/2309/93: Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (Official Journal L 214, 24/8/1993 p. 1 – 21). [German and English Version]

Regulation EC/726/2004: Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Official Journal L 136, 30/4/2004 p. 1 - 33). [German and English Version]

Regulation EC/141/2000: Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (Official Journal L 18, 22/1/2000 p. 1 - 5). [German and English Version]

Regulation EC/1084/2003: Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State (Official Journal L 159, 27/6/2003 p. 1 - 23). [German and English Version]

Regulation EC/1085/2003: Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93 (Official Journal L 159, 27/6/2003 p. 24 - 45). [German and English Version]

Regulation EEC/1768/92: Council Regulation No (EEC) 1768/92, of 18 June 1992, concerning the creation of a supplementary protection certificate for medicinal products (Official Journal L 182, 2/7/1992 p. 1 – 5). [German and English Version]

NtA Vol. 2A: The Rules Governing Medicinal Products in the European Union - Vol. 2: Notice to Applicants. Vol. 2A: Procedures for marketing authorisation.

NtA Vol. 2C: The Rules Governing Medicinal Products in the European Union - Vol. 2: Notice to Applicants. Vol. 2C: Regulatory Guidelines. Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) (October 2003).

PAEDIATRIC PROPOSAL, 2004: Proposal for a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/83/EC and Regulation (EC) No 726/2004, published **29. September 2004**. [<http://pharmacos.eudra.org/F2/Paediatrics>]

PAEDIATRIC PROPOSAL FAQ, 2004: Regulation on medicines for children: frequently asked questions, published **28. October 2004**. [<http://pharmacos.eudra.org/F2/Paediatrics>]

Common Position 61/2003: Common Position (EC) No 61/2003 adopted by the Council with a view to the adoption of a Directive 2003/.../EC of the European Parliament and of the Council of ...amending Council Directive 2001/83/EC on the Community code relating to medicinal products for human use (2003/C 297 E/02). **29 September 2003**.

Commission Communication 98/C 229/03: Commission communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03). **22 July 1998**.

ECJ C-368/96: Judgement of the Court, Fifth Chamber, in Case C-368/96, Reference to the Court under Article 177 of the EC Treaty by the High Court of Justice (England & Wales), Queen's Bench Division, for a preliminary ruling in the proceedings pending before that court between The Queen and The Licensing Authority established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex

parte: Generics (UK) Limited, intervener: E.R. Squibb & Sons Limited, between The Queen and The Licensing Authority established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte: The Wellcome Foundation Limited, and between The Queen and The Licensing Authority established by the Medicines Act 1968 (acting by The Medicines Control Agency), ex parte: Glaxo Operations UK Limited and Others, intervener: Generics (UK) Limited. **3 December 1998.**

ECJ C-106/01: Judgement of the Court, Sixth Chamber, in Case C-106/01, Reference to the Court under Article 234 EC by the Court of Appeal (Civil Division) (England and Wales) for a preliminary ruling in the proceedings pending before that court between The Queen on the application of Novartis Pharmaceuticals UK Ltd and The Licensing Authority established by the Medicines Act 1968 (acting by the Medicines Control Agency), and SangStatUKLtd, and Imtix-SangStat UK Ltd, on 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 (OJ, English Special Edition 1965-1966, p. 20), as amended by Council Directives 87/21/EEC of 22 December 1986 (OJ 1987 L 15, p. 36), 89/341/EEC of 3 May 1989 (OJ 1989 L 142, p. 11) and 93/39/EEC of 14 June 1993 (OJ 1993 L 214, p. 22). **29 April 2004.**

ECJ C-36/03: Judgement of the Court, Second Chamber, in Case C-36/03, Reference for a preliminary ruling under Article 234 EC from the High Court of Justice of England and Wales, Queen's Bench Division (Administrative Court), made by order of 23 December 2002, received at the Court on 3 February 2003, in the proceedings The Queen, on the application of: Approved Prescription Services Ltd, vs. Licensing Authority, acting by the Medicines and Healthcare products Regulatory Agency, interested party: Eli Lilly & Co. Ltd. **9 December 2004.**

ECJ C-74/03: Judgement of the Court, Second Chamber in Case C-74/03, Reference for a preliminary ruling under Article 234 EC from the Østre Landsret (Denmark), made by decision of 14 February 2003, received at the Court on 19 February 2003, in the proceedings SmithKline Beecham plc vs. Lægemeddelstyrelsen, Interveners: Synthron BV and Genthon BV. **20 January 2005.**

EMEA/CPMP/2347/03: Committee for Proprietary Medicinal Products. April 2003 Plenary Meeting, Monthly Report (EMEA/CPMP/2347/03), London, **02.05.2003**.

MRFG, 2002: Applications under Annex II of Regulation (EC) No 541/95 in Mutual Recognition Procedures. Member States Recommendations. Final version: June 1999. Last update **July 2002**.

b) Secondary Literature and Internet Resources

BOGAERT, 2004: P. Bogaert, EU pharmaceutical legislation: an overview of the main changes, *Global Counsel Life Sciences Handbook 2004/05*, **2004**, 41-45.

[www.practicallaw.com/lifesciences]

[www.cov.com/publications/download/oid58138/494.pdf]

BRAKE, 2004: B. Brake, Generische Zulassung von BioTech-Arzneimitteln? - Biosimilars! Presentation given at the DGRA workshop "Intellectual Property Rights - IP - for medicinal products - MP", Bonn, **17. November 2004**. [www.dgra.de]

BÜTTRICH, 2004: A. Büttrich, Intellectual Property Rights for medicinal products. Änderungen nach dem Review 2004. III. Schutz für Line Extensions? Presentation given at the DGRA workshop "Intellectual Property Rights - IP -for medicinal products - MP", Bonn, **17. November 2004**. [www.dgra.de]

CORREA, 2002: C. M. Correa, Protection of Data Submitted for the Registration of Pharmaceuticals: Implementing the Standards of the TRIPS Agreement, South Centre, Geneva, Switzerland, **2002**.

CRA REPORT, 2004: Innovation in the pharmaceutical sector. A study undertaken for the European Commission by Charles River Associates, **8. November 2004**. [pharmacos.eudra.org/F2/pharmacos/docs/

[Doc2004/nov/EU%20Pharma%20Innovation_25-11-04.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/nov/EU%20Pharma%20Innovation_25-11-04.pdf)]

DE RIDDER, 2003: J. de Ridder, Data Exclusivity: Further Protection for Pharmaceuticals, **June 2003**. [<http://www.findlaw.com.au/article/9200.htm>]

EGA, 2004: Evergreening of Pharmaceutical Market Protection, Homepage of the EGA - European Generic medicines Association, seen **January, 2005**. [<http://www.egagenerics.com>]

FARACIK, 2002: B. Faracik, The right to health and right to intellectual property in the EU. Analysis of the internal and external policies, Master Thesis, Raoul Wallenberg Institute, Lund University, **2002**.

GENERICS BULLETIN, 2004: Europe reaches agreement on revisions to pharma law, Generics Bulletin, **16. January 2004**. [<http://www.egagenerics.com>]

HORTON, 2004a: L. Horton *et al.*, The aims of new European Union pharmaceutical rules, *Pharma Marketletter* **27. 09. 2004**, 24-25. [www.hhlaw.com/articles/1574_351%20PML%2022-9-04.pdf]

HORTON, 2004b: L. R. Horton, J. Mailly, K. Goecke, Raft of Regulations, *manufacturing chemist* **June 2004**, 20-21. [www.manufacturing-chemist.info] [http://www.hhlaw.com/articles/1479_351%20MC%20June%2004%202.pdf]

IDRAC 'GENERIC', 2004: How to market generics (European Union), IDRAC-database text, **Dec. 2004**. [www.idrac.com]

IDRAC 'EU REVIEW', 2005: New Pharmaceutical Legislation (European Union), IDRAC-database text, **Feb. 2005**. [www.idrac.com]

KINTZEL, 2004: B. Kintzel, Review of the EU Pharmaceutical Legislation ("Review 2001"), DGRA study course, Module 9 - International Registration Procedures, Bonn, **January 23 and 24, 2004**. [<http://www.dgra.de>]

LARSON, 2001: E. Larson, Evolution of IPR and Pharmaceutical Discovery and Development, presentation given at the conference: "Intellectual Property Rights: How Far Should They Be Extended?", organised by The National Academies, Committee on Intellectual Property Rights in the Knowledge-based Economy, **22 October 2001**. [www7.nationalacademies.org/step/Larson_ppt.ppt.]

LE COURTOIS, 2005: P. Le Courtois, Road Map to 2010: The future of self-care. Part II: Making the Centralised Procedure a real opportunity for the self-care industry. Getting the dossier right, AESGP (Association Européenne des Spécialités Pharmaceutiques Grand Public, Association of the European Self-Medication Industry) Member's Meeting, London, **19-20 January 2005**. [<http://www.aesgp.be>]

LIESE, 2004: P. Liese, Bessere Arzneimittel für Kinder - Haltung des Europäischen Parlamentes, Sonderdruck aus: *Arzneim. Forsch. - Drug Res.* **2004**, *54*, 29-32. [www.paul-martini-stiftung.de/de/publikationen/04-01.pdf]

LINKLATERS IP NEWSLETTER, 2005: J. Jones-Parry, I. Karet, Linklaters Intellectual Property Newsletter, **January 2005**, *38*, 1-12, esp. p.1-2. [<http://www.linklaters.com>]

MAILLY, 2005: J. Mailly, Future European Pharmaceutical Legislation: Key Provisions, Status, & Controversial Issues, Pharmaceutical Law Europe Conference, London, 26-27th January 2005. [<http://www.hhlaw.com/>]

MLX 309, 2004: MHRA (Medicines and Healthcare products Regulatory Agency), Consultation Letter MLX 309. Implementation of Revised EU Medicines Legislation: Implementing the "2001" Review, **29 July 2004**. [<http://www.mhra.gov.uk>]

MLX 309 OUTCOME, 2004: MHRA (Medicines and Healthcare products Regulatory Agency), Outcome of the consultation exercise MLX 309 on early implementation of certain provisions of the revised EU Medicines Legislation, **29 July 2004**. [<http://www.mhra.gov.uk>]

MLX 317, 2005: MHRA (Medicines and Healthcare products Regulatory Agency), Consultation Letter MLX 317. Implementation of Revised EU Medicines Legislation: Implementing the "2001" Review, **22 March 2005**. [<http://www.mhra.gov.uk>]

MLX 317 ANNEX, 2005: MHRA (Medicines and Healthcare products Regulatory Agency), Consultation Letter MLX 317. Implementation of Revised EU Medicines Legislation: Implementing the "2001" Review. Annex A: Review of EU Medicines

Legislation – Proposals for Implementation, **22 March 2005**.
[<http://www.mhra.gov.uk>]

PERRY, 2004: G. Perry, IP Developments In the EU 2003 - 2004, presentation given at the IGPA Annual Conference, IP Session, Prague, **28 June 2004**.
[<http://www.egagenerics.com>]

PUGATCH, 2004: M. P. Pugatch, Intellectual property and pharmaceutical data exclusivity in the context of innovation and market access, *ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines*, Bellagio, **12-16 Oct. 04**. [www.iprsonline.org/unctadictsd/bellagio/docs/Pugatch_Bellagio3.pdf]

STRÄTER, 2004: B. Sträter, Änderungen nach dem Review 2004. Vorgaben für die 14. AMG- Novelle. Presentation given at the DGRA workshop "Intellectual Property Rights - IP -for medicinal products - MP", Bonn, **17. November 2004**. [www.dgra.de]

STRÄTER, 2005: B. Sträter, Patente und Unterlagenschutz. Presentation of the Anwaltskanzlei Sträter, Kronprinzenstraße 20, 53173 Bonn, **May 2005**. [www.KanzleiStraeter.de]

THROM, 2004: S. Throm, Aktuelle Entwicklungen in der EU, *Arzneim. Forsch. - Drug Res.* **2004**, 54, 28. [www.paul-martini-stiftung.de/de/publikationen/04-01.pdf]

VfA, 2004: Patentschutz - Garant für therapeutischen Fortschritt, Homepage of the VfA - Verband forschender Arzneimittelhersteller, seen **January, 2005**. [<http://www.vfa.de/de/politik/artikelpo/patentschutz.html>]

VIGENSCHOW, 2004: H. Vigerschow, Produktentwicklung von Generica während der Patentlaufzeit. Presentation given at the DGRA workshop "Intellectual Property Rights - IP -for medicinal products - MP", Bonn, **17. November 2004**. [www.dgra.de]