

Protection of fixed-dose combination drugs by patent term extension

a comparative study between the US and EU

Master Thesis

Author(s):

Heyder, Christoph

Publication date:

2009

Permanent link:

<https://doi.org/10.3929/ethz-a-006166804>

Rights / license:

[In Copyright - Non-Commercial Use Permitted](#)

MAS ETH IP
ETH ZURICH
WEINBERGSTRASSE 43
8006 ZURICH



Master thesis

PROTECTION OF FIXED-DOSE COMBINATION DRUGS BY PATENT TERM EXTENSION – A COMPARATIVE STUDY BETWEEN THE US AND EU

Dr. Christoph Heyder

25. September 2009

1. Advisor: Dr. H. Kjellsaa-Berger
2. Advisor: Dr. U. Szapl

ACKNOWLEDGEMENTS

My sincere appreciation goes to my supervisors Dr. HannyKjellsaa-Berger and Dr. UweSzipl for their helpful discussion and supportive comments, and to Dr. Herbert Laederach, Andrea Bürer, Caroline Frischknecht, and last but not least to my semester colleagues from the MASIP who truly made this a memorable year. Also, I would like to thank Dr. Ina vom Feld for her help in providing the French court decision Novo Nordisk v. INPI.

TABLE OF CONTENTS

Abbreviations.....	4
1. Introduction.....	5
1.1 The Drug Price Competition and Patent Term Restoration Act.....	5
1.1.2 The Drug Price Competition Title.....	6
1.1.3 Patent Term Restoration.....	7
1.2 European Council Regulation 1768/92.....	8
1.3 Fixed-dose combination drug products.....	10
1.3.1 Patent term extension for FDCs.....	12
2. Statute law and case law in the US.....	13
2.1 The definition of ‘product’ pursuant to 35 USC §156.....	13
2.2 EMLA Topical Cream.....	13
2.3 Arnold Partnership v. Dudas (“Vicoprofen”).....	15
2.4 Fisons v. Quigg – a PTE for a new medical indication?.....	17
2.5 A PTE Application for a synergistic FDC (“ Symbicort”).....	19
3. Statute law and case law in the EU.....	23
3.1 The definition of ‘product’ in EU Regulation 1768/92.....	23
3.2 The definition of ‘active ingredient’.....	24
3.3 The ECJ’s Gliadel decision.....	25
3.3.1 Opinion of the Advocate General.....	26
3.3.2 Final judgment.....	27
3.4 After the Gliadel decision.....	29
3.4.1 New indication – Yissum University.....	29
3.4.2 Combination of Somatotropin and histidin - Novo Nordisk.....	29
3.5 ‘Protected by a basic patent in force’.....	30
3.5.1 Takeda Chemical Industries.....	30
3.5.2 Gilead Sciences Inc.....	31
4. Discussion.....	33
5. Conclusion.....	36
Bibliography.....	37

ABBREVIATIONS

ANDA	Abbreviated New Drug Application
BGH	German Federal Supreme Court (Bundesgerichtshof)
CAFC	United States Court of Appeals for the Federal Circuit
ECJ	European Court of Justice
FDA	United States Food and Drug Administration
FDC	Fixed-Dose Combination Drug
NCE	New Chemical Entity
NDA	New Drug Application
PTE	Patent Term Extension
PTO	United States Patent and Trademark Office
SPC	Supplementary Protection Certificate

1. INTRODUCTION

The development of new molecular entities is a high-risk process and requires a substantial amount of time and financial funding. The cost of introducing an innovator drug to the market is estimated at 0.8-1.2bn USD, and the development time including clinical trials and regulatory approval often exceeds 10 yrs. This leads to a significantly shortened effective patent term. In order to allow research-based pharmaceutical companies to recoup their investment made for the development of new drug products, legislative acts were created in the US and the EU for the extension of the patent term. However, innovation in the pharmaceutical area often does not involve the development of new drug entities (NCEs), but includes new indications for known drugs and new formulations with improved pharmacologic profiles.¹ Moreover, since the number of approved NCEs is currently in the decline, the reformulation of already known and tested drugs into a fixed-dose combination may provide an important strategy for pharmaceutical companies to develop new drug products and to maximize returns.² Therefore, it is important to assess how patent term restoration regimens apply to drug products that are based on already characterized drug compounds, as is the case for many fixed-dose combination drugs (FDCs). In the following, an introduction shall be provided to the legislative acts for patent term extension in the US and the EU.

1.1 THE DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT

The Drug Price Competition and Patent Term Restoration Act of 1984³, also known as the “Hatch-Waxman Act”, was one of the most important amendments of US patent law and introduced significant changes to the healthcare industry. The Act was created to encourage innovation by research-based pharmaceutical companies, and to allow a speedy entry of lower-cost generic drugs to the market. Particularly, the costs for R&D had been on the rise for decades, as had the time to bring a new drug product to the market.⁴ In the late 1970's, research intensive pharmaceutical companies therefore became increasingly concerned that the effective patent term of their marketed drug products were being eroded by long periods of regulatory review by the FDA. In 1978, President Carter initiated a major domestic policy review on industrial innovation, which concluded with a recommendation to restore the patent term for pharmaceuticals and any other product that required regulatory approval in order to compensate for effective patent life lost during regulatory procedures.⁵ At that time, however, market approval for generic versions of original drugs whose patents had expired generally required filing of an NDA and clinical testing for safety and efficacy by the generic drug maker, even if the drug was chemically identical to the original.⁶ Therefore, not many generic drugs were available in the US, leading to a call for extended approval of generic drug products by a variety of different interest groups, including consumers and generic drug manufacturers. When the bill was passed by Congress in 1984, the patent term restoration provisions had been complemented by a drug price competition title to achieve a delicate balance

between the opposing interests of originator and generic pharmaceutical companies. On the one hand, generic market entry was significantly facilitated due to the possibility of filing abbreviated new drug applications (ANDAs). On the other, research-based pharmaceutical companies had been granted the possibility to extend the effective patent life of some of their innovator products which previously had been shortened by extended periods of regulatory review.

1.1.2 THE DRUG PRICE COMPETITION TITLE

Title I of the Act introduced far-reaching and complex changes for the approval procedure of generic drugs. The ANDA procedure restricted the FDA to only prescribe bioavailability studies on relatively small groups of patients, and had set an additional incentive for accelerated generic entry by awarding a 180-day period of market exclusivity for the first company to file an abbreviated application for a particular drug product. Furthermore, the Patent Act was modified by creating a statutory exemption from claims of patent infringement by allowing generic manufacturers to commence their work on obtaining market approval in accordance with regulatory procedures before the patent of the originator drug had actually expired. However, a five-year data exclusivity for NCEs was introduced, providing that once an NCE was approved, authorization for the generic drug could not be obtained for a period of 5 years. In addition, generic drug makers had to comply with a new certification process to state their intention when applying for an ANDA.⁷ These certifications were respectively termed paragraph I, II, III, and IV certifications. An ANDA under paragraphs I or II applies to the situation where no relevant patent information is available or the patent has expired and can be subject to approval immediately after meeting all applicable regulatory and scientific requirements. An ANDA certified under paragraph III must, even after meeting the regulatory and scientific requirements, wait for approval until the listed patent of the drug expires. If however marketing approval is obtained before expiry of the patent term, an artificial infringement situation is created where the would-be generic drug maker challenged the validity of the patent by a paragraph IV certification.⁸ If the originator drug company decides to defend the patent within a 45-day time period, an automatic stay (up to 30 months) would be triggered during which the FDA could not approve the generic drug. If the patent was considered to be valid by the courts, market authorization would be denied until expiry of the patent. If the patent was however nullified in an invalidity action, market authorization of the generic could be granted given that the generic drug maker complied with the other regulatory and scientific requirements. The 'link' between the ANDA and the brand name manufacturer's patent is provided by the 'Orange Book', where holders of a New Drug Application (NDAs) are required to list relevant patents that would potentially be infringed by a generic drug.⁹ Taken together, far reaching changes had been introduced by Title I of the Hatch-Waxman Act in regard to the entry of generic drugs into the marketplace.

1.1.3 PATENT TERM RESTORATION

Title II of the Hatch Waxman Act was created to set incentives for research-based pharmaceutical companies and to compensate them for effective patent life lost due to lengthy regulatory procedures. This title amended US patent law and provided for a patent term extension of human pharmaceutical drugs, medical devices which are subject of approval by health authorities, and food and color additives. Under 35 U.S.C. §156a, a PTE can be granted on compound, combination, process, and method of use patents if a number of requirements are met¹⁰:

- (1) the term of the patent has not expired
- (2) the term of the patent has not been extended before
- (3) an application for extension is submitted by the owner of record of the patent or its agent
- (4) the product has been subject to a regulatory review period before its commercial marketing or use
- (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the law under which such regulatory review period occurred

The extension of the patent term under §156 is subject to the limitation that only one extension can be granted per patent, even if the patent claims multiple approved products. The patent extension application must be submitted within 60 days after the approval of a new drug application by the FDA. If the patentee is a different person from the rightholder of the market authorization, the patentee is required to submit an indication of a link to the MA-holder, for instance a licensing contract. The extension period is calculated as follows:

IND Submission --- (a) ---> NDA Submission --- (b) ---> NDA Approval

$$\text{PTE} = 0.5(a) + (b)$$

IND = Investigational New Drug Application, NDA = New Drug Application

(a) = time between IND submission and NDA submission

(b) = time between NDA submission and NDA Approval

Thus, the PTE amounts to half the time between IND and NDA submission, and all of the time between NDA submission and NDA approval. Due diligence is required from the applicant during the approval process, and the time period where the applicant did not comply with this requirement during the approval process is deducted from the overall extension term granted. The PTE is further limited to a maximum of 5 years, and cannot extend for a period that is more than 14 years after NDA approval.

1.2 EUROPEAN COUNCIL REGULATION 1768/92

After patent term restoration had been introduced in the US in 1984 and subsequently in Japan in 1988, there was increasing pressure on the European pharmaceutical industry to also demand for an extended patent term for pharmaceutical inventions.¹¹ In 1987, Directive 87/21/EEC¹² had already introduced a data exclusivity regimen which protected the data of the originator pharmaceutical companies against the generic competition. In addition, the Directive provided a procedure for abridged applications for 'essentially similar' products by introducing a harmonized approval route for the generic industry in the EU. However, different studies suggested that the effective patent life of approved pharmaceutical drug products had declined significantly during the last decades. For instance, it was calculated by Suchy¹³ that the effective patent term of approved new drug entities in Germany between 1979 and 1986 was 10.1 years calculated from market authorization for a 20-year patent term. The same time period further declined to below 10 years (9.6 years) around 1990.¹⁴ According to a British study, the effective patent term for approved drug products in the U.K. was however still 11.4 years from the time period of 1984 to 1988.¹⁵ The decline of the effective patent life of approved pharmaceutical products, and the argument that the cost for research and development for new and innovative pharmaceuticals could not be recovered by the industry, led to a Proposal by the EC Commission in 1990 for a supplementary protection certificate (SPC) to extend the patent term of medicinal products.¹⁶ At the same time, France was already in the process of introducing its own legislature for a protection certificate for medicinal products, which was enacted in 1990. Also, Italy followed the French initiative and introduced SPC protection in 1991, adding further pressure on the Commission to harmonize European law. The Commission stated: "The basic objectives of this proposal for a Regulation ... concern the requirements relating to the proper functioning of the internal market, improvement of our competitiveness as compared with that of our trade partners and the encouragement of research and development in the health field".¹⁷ The Proposal intended that the certificate should be a sui generis right¹⁸ to avoid conflicts with the 20-year patent term specified in Article 63 of the European Patent Convention (EPC). On behalf of concerns of the German government, however, a revision conference was called and Article 63 was amended on December 17, 1991 to bring the EPC into conformity with the new initiative.¹⁹ On January 2, 1993, Council Regulation 1768/92 concerning the creation of a supplementary protection certificate for medicinal products went into force. Thereby, the newly created sui generis right granted to the owner the same privileges and obligations as a patent, with the important difference that it does not extend the entire scope of the patent, but only the 'medicinal product' for which market authorization was obtained due to a regulatory approval procedure. According to Article 3 of the Regulation, a list of requirements has to be met to obtain SPC protection:

- (a) the product is protected by a basic patent in force
- (b) a Market Authorization was issued in the country the SPC is sought for
- (c) no SPC has been granted before for the product in that country
- (d) the MA has to be the first MA of the product as a medicine in the member state

According to Article 3, the patent owner must choose a 'basic patent' in each member state protecting the drug product authorized pursuant to Directive 2001/83 or centrally under Regulation 726/2004. The SPC is applied for in each member state and only one SPC can be granted per product and patent owner in that member state. In case of multiple patent holders, each one may obtain a separate SPC based on the same marketing authorization. Furthermore, a recent ECJ ruling provides that this is possible even if the first SPC has already been granted.²⁰ In contrast to US practice, multiple SPCs may be granted on the basis of the same patent. The application must be made within 6 months from the grant of marketing authorization in that country, or within 6 months of patent grant, whichever is later. The aim of the Regulation 1768/92 is to give 15 years of protection for a medicinal product from the first market authorization, whereby the date of patent grant and the actual time used for regulatory approval are not considered. The SPC takes effect on expiry of the basic patent, and the duration is calculated as follows²¹:

$$\text{SPC duration} = ([\text{date of 1st MA in the EEA}] - [\text{date of filing of basic patent}]) - 5 \text{ years}$$

MA = market authorization; maximum SPC duration = 5 years

Therefore, if the first market authorization is granted between a time period of 5 and 10 years from patent filing, a combined SPC and patent protection term of 15 years is ensured. However, if approval takes longer than 10 years from filing the patent, SPC duration is capped at 5 years. Although a national marketing authorization is a prerequisite for obtaining a SPC, its term is calculated using the earlier market authorization if there has been an earlier approval in another EEA country. This was based on the rationale that SPCs relating to the same product and based on the same patent shall expire on the same day throughout Europe. Determination of the first market authorization, therefore, is of central importance determining the duration of the SPC. Moreover, according to Article 4, the scope of an SPC extends "only to the product covered by the authorization to place the corresponding medicinal product on the market and for any use of the product as a medicinal product that has been authorized before the expiry of the certificate". Since the scope of a SPC is limited to the product covered by the authorization only, a key question is how 'product' is defined in this context. The European Court of Justice has decided that the scope of an SPC may encompass more than just the single form of the active ingredient that is included in the authorized and marketed medicinal product, and covers salt and ester derivatives within its scope of protection.²² The "salt problem" and the scope of SPC protection has been thoroughly reviewed by Thomsen (2000).²³ In 1996, Regulation 1610/96 introduced SPC protection for plant

protection products, which also was effected by deterioration of the effective patent term. Furthermore, Regulation 1901/2006 on medicinal products for pediatric use introduced an additional 6 months of SPC extension for pharmaceutical companies which engaged in a pediatric investigation plan. Thus, SPC protection for medicinal products is extendable by a maximum of 5.5 years with the objective to provide incentives for clinical research in the pediatric field. Recently, SPC Regulation 1768/92 was codified as EC Regulation No. 469/2009 of May 6, 2009.

1.3 FIXED-DOSE COMBINATION DRUG PRODUCTS

Innovation in the pharmaceutical area is often based on already existing drug entities, and includes new indications for known drugs and new formulations with improved pharmacologic profiles.²⁴ For instance, the combination of active ingredients with complementary pharmacological activity has considerable potential for providing improved therapeutic regimens for patients in various fields of disease. Thereby, fixed-dose combination drug products are the combination of two different active ingredients in one single form of pharmaceutical administration. The dose of each active ingredient within the combination preparation is fixed, thus the term 'fixed-dose' combination product (FDC).²⁵ FDCs may provide significant benefits to patients in the area of infectious diseases, asthma, and hypertension. For instance, FDCs are considered to significantly improve long-term antiviral drug regimens to control HIV, especially in resource limited countries. Suppression of viral load by highly active antiretroviral therapy (HAART) requires the administration of multiple different drugs in combination (three on average), which results in an increased pill burden (6 or more tablets per day depending on the formulation of each individual drug).²⁶ A high pill burden may lead to a sub-optimal adherence to the therapeutic regimen and thus, a reduced treatment response.²⁷ Long-term adherence to HAART is one of the challenges in fighting HIV infection, particularly in countries of the developing world, and it has been a goal of the pharmaceutical industry to simplify drug administration by developing a once per day treatment schedule.²⁸ To implement a simplified regimen, the pharmaceutical companies Bristol-Myers Squibb and Gilead Sciences formed a joint-venture to develop the first three-part fixed-dose antiretroviral product Atripla, a fixed-dose combination of Bristol-Myers Squibb's Sustiva (efavirenz, a non-nucleoside reverse transcriptase inhibitor) and Gilead's fixed-dose product Truvada (tenofovir and emtricitabine, two nucleoside reverse transcriptase inhibitors). Atripla was approved by the FDA in 2006, and by 2008 has become the most prescribed antiretroviral drug for patients initiating therapy in the US.²⁹

The treatment of chronic airway diseases is another important area where combination drugs are considered to have a significant advantage. For instance, the long-term therapy of persistent asthma often requires the use of two inhalers, such as the combination of inhaled corticosteroid (ICS) and a long acting beta-2 agonist (LABA).³⁰ Scientific and clinical data support the complementary mechanisms of action of ICSs and LABAs when administered in a single inhaler, achieving a significant reduction in

exacerbations and an effective control of chronic airway inflammation.³¹ GlaxoSmithKline's blockbuster asthma product Advair (Seretide outside the US) combines the ICS fluticasone (Flovent) and the LABA salmeterol (Serevent), and is the best selling FDC product with global sales of US\$ 7.4bn in 2008³². Furthermore, at least one meta-study suggests a synergistic effect when fluticasone and salmeterol are combined in a single inhaler.³³ AstraZeneca's competing product Symbicort, a combination of the ICS budesonide and the LABA formoterol, was launched in the US in 2007 (in Europe since 2001), and achieved global sales of US\$ 2 billion in 2008.³⁴ Further ICS/LABA combinations, such as SkyePharma's Flutiform (fluticasone/ formoterol) and Novartis/Schering-Plough's MFF258 (mometasone/formoterol), are expected to launch in 2010.

The field of cardiovascular diseases is another major area where multi-drug regimens are a well-accepted treatment paradigm. For instance, two out of three hypertensive individuals require two or more antihypertensive agents selected from different drug classes, such as diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor antagonists, and calcium-channel blockers. Thereby, the combination of active ingredients with different pharmacological effects provides a more effective reduction of blood pressure than a single agent alone.³⁵ For instance, the antihypertensive effects of an ACE-inhibitor and a calcium channel blocker are additive, but each drug has a different side effect profile. Since the same reduction of blood pressure can be achieved with a lower dosage of each drug, the exposure to adverse side effects is reduced due to the non-additive nature of the side effect profiles, and an increased therapeutic ratio is achieved.³⁶ Other effects that can be achieved by using combinations are potentiation and cancellation. The phenomenon of potentiation means that an active ingredient is combined with a therapeutically inactive constituent that enhances the effect of the active substance. For instance, hydrochlorothiazide (HCT) potentiates the effect of other anti-hypertensive drugs and increases the therapeutic ratio.³⁷ The phenomenon of cancellation reduces adverse side effects of one drug by addition of another, e.g. by adding an ACE-inhibitor to counteract the hypokalemic effect of thiazide diuretics.³⁸ Novartis' Exforge combines the blockbuster drug Diovan (valsartan), an angiotensin receptor antagonist, and the calcium channel blocker amlodipine, and was launched in the US and Europe in 2007, accounting for global sales of US\$ 406 million in 2008³⁹. Also, the triple-drug combination Exforge-HCT (valsartan/amlodipine/hydrochlorothiazide) has been approved by the FDA in 2009.

Taken together, FDCs are more convenient to administer and provide better compliance with a particular treatment regimen. This is particularly important in the field of infectious and chronic diseases, where long-term compliance with a treatment regimen is necessary to effectively control the disease. Importantly, FDCs are capable of providing a reduced toxicity profile due to a dose reduction of the individual constituents. In addition, a combination of active ingredients may show different pharmacological effects in combination compared to their individual form. In the case of a synergistic action, the therapeutic efficacy of a combination is greater than the sum of its constituents. Moreover,

the phenomenon of cancellation can be used to eliminate certain adverse side effects, thus making treatment more tolerable for the patient.

1.3.1 PATENT TERM EXTENSION FOR FDCS

As an improvement invention, FDCs are eligible for a 20-year term of patent protection if they satisfy the requirements of novelty, inventive step, and industrial application. Combination products may either be claimed as part of a patent for a novel pharmaceutical compound, or in a subsequent patent if an unexpected effect can be shown, such as increased safety or increased efficacy. Such an unexpected effect can be a synergism, or one of the other mechanisms discussed in the previous section that can be encountered when different drugs are combined into a FDC product. Interestingly, FDCs are similar to new drug entities from a regulatory perspective, regardless if the individual drugs have been approved separately for commercialization before. In order to qualify for regulatory approval, the effect of the combination has to be compared to that of the single drugs alone, which requires at least three-group trials, or even four-group trials if a placebo is included. This strict regulatory view on FDCs definitely is necessary to rule out a negative effect of the combination, and to show that the new drug has a benefit for the patient. However, this view also implies that an FDC is to be treated as a new entity, despite the fact that the individual constituents may have marketed before. Thus, it is a relevant question if patented FDCs with already known and approved constituents can benefit from patent term extension regimens in the US and the EU.

2. STATUTE LAW AND CASE LAW IN THE US

2.1 THE DEFINITION OF 'PRODUCT' PURSUANT TO 35 USC §156

According to 35 USC §156(a) the term of a patent shall be extended if, inter alia, the product has been subject to a regulatory review period before its commercial marketing or use. Furthermore, §156(a)(5)(A) provides that the

“permission for the commercial marketing or use of the product .. is the first permission for the commercial marketing or use of the product under the provision of law under which such regulatory review occurred”

The term 'product' is further defined in §156(f):

“(f) For purposes of this section:

(1) the term “product” means:

(A) A drug product ...

(2) The term “drug product” means the active ingredient of -

(A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act) ...

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.”

In the context of FDCs, the definition of 'product' was applied for the first time by the PTO in 1994 for the drug product “EMLA Topical Cream”, which shall be reviewed in the following section.

2.2 EMLA TOPICAL CREAM

In a 1994 decision, the PTO for the first time addressed the issue of PTEs for combinations of active ingredients where each of the active ingredients had previously been approved separately for commercial marketing.⁴⁰ The Swedish pharmaceutical company Astra had applied for an extension of the term of their US Patent No. 4,529,601 for a mixture containing lidocaine and prilocaine in specific weight proportions, for which they had received market authorization by the FDA as a topical cream („EMLA cream”⁴¹) for local anesthesia. The two active ingredients were well-known topical anesthetics and had previously received market approval independently. Astra asserted that EMLA cream contains lidocaine and prilocaine at specific proportions such that the melting point for the two compounds is minimized, resulting in an eutectic mixture of the two compounds which allows the cream to be in liquid rather than in crystal form at room temperature. This particular characteristic permits higher concentrations of active ingredients in the topical cream. Astra claimed that the specific mixture of the two local anesthetics in EMLA cream is a distinct and novel active ingredient. Therefore, market approval for EMLA cream would be the first marketing authorization of the product as required by §156(a)(5)(A). The PTO determined the meaning of

the statutory language used in §156, particularly the definition of the term ‘product’ mentioned in §156(a)(5)(A), which is explicitly mentioned and subject to definition in §156(f):

“(1) the term “product” means:

(A) A drug product. ..

(2) The term “drug product” means the active ingredient of -

(A) anew drug ..

including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient.”⁴²

The PTO comments that the language of the statute states “active ingredient”, not “active ingredients”. The distinction between the singular and plural form is a key element for construing the term active ingredient, and strongly suggests that each active ingredient has to be assessed separately in terms of a prior market authorization. This is further supported by the fact that an active ingredient may be used “in combination with another active ingredient”. In the hypothetical case that the plural, not the singular had been used in the statutory language, it could have been validly argued that the mixture of the two active ingredients lidocaine and prilocaine was indeed a new and previously not approved product. In that case, the combination could have qualified as a new product since market approval had only been granted for the single entities. However, would the term “drug product” be interpreted as containing more than one active ingredient, the inclusion “any salt or ester of the active ingredient” would not make much sense, since there cannot be a salt or an ester for more than one ingredient⁴³.

Interestingly, for the product EMLA cream, the FDA had waived the applicability of the fixed combination drug policy, which usually requires comparative studies of the combination product to the single active ingredients. Astra asserted that the FDA had therefore acknowledged that EMLA cream did not have two active ingredients⁴⁴. However, the waiver of the combination drug policy was due to the difficulty of obtaining appropriate single ingredient controls, and not because the FDA considered EMLA cream to be a single chemical entity. A previous communication from the FDA had explicitly rejected the single-ingredient character: “..EMLA cream contains the two previously-approved drugs of lidocaine and prilocaine rather than [...] a new chemical entity resulting from these two active ingredients.”⁴⁵ Therefore, the eutectic mixture was considered sufficiently unique to warrant an exception from comparative testing, but was not a new active ingredient in the understanding of the FDA. According to the FDA's drug classification system⁴⁶, class I drugs are defined as new chemical entities (NCEs), i.e. the active moiety (that part of the compound responsible for the therapeutic effect), which has never been marketed before in the US either as an individual drug or in combination. Type 1 drugs are contrasted to other types, such as new salts, esters, or non-covalent derivatives of active moieties (Type 2), new formulations

(Type 3), new combinations of drugs previously not marketed together (Type 4), new manufacturer (Type 5), new indications (Type 6), and already marketed drugs but without an approved NDA (Type 7). The PTO took note that the only evidence available to Congress that patent time was lost during a regulatory review period is data for “class I, new chemical entity drugs”. This suggests that patent term extension can only be granted for NCEs, not for the other chemical types. Therefore, in order to be eligible for patent term extension, the patent must claim the active ingredient of a new drug, as a single entity or in combination with another active ingredient. Patent term restoration for EMLA cream was denied.

2.3 ARNOLD PARTNERSHIP V. DUDAS (“VICOPROFEN”)

A similar case where patent term extension was sought for a combination of two previously approved drugs was decided by the Federal Court of Appeals in 2004⁴⁷. Arnold Partnership was the holder of U.S. Patent No. 4,587,252 (“the '252 patent”) on a pharmaceutical composition consisting of the semi-synthetic opioid hydrocodone and the nonsteroidal anti-inflammatory drug ibuprofen.⁴⁸ The composition was commercialized as Vicoprofen, and was the first combination of hydrocodone and ibuprofen on the market. The PTO denied extension of the term for the '252 patent, because Vicoprofen did not fulfill the “first commercial marketing” requirement pursuant to §156(a)(5)(A). The PTO reasoned that both hydrocodone and ibuprofen had received market approval either alone or in combination with other active ingredients before.⁴⁹ Hydrocodone bitartrate had been commercialized previously in combination with other active ingredients, including acetaminophen and aspirin, whereas the pain reliever ibuprofen had been marketed as a single drug alone. Arnold then filed suit in the District Court for the Eastern District of Virginia under the Administrative Procedure Act⁵⁰ challenging the denial for patent term extension. The District court however upheld the PTO's statutory interpretation and confirmed the denial of extension of the '252 patent term.⁵¹ Arnold filed an appeal before the Court of Appeals for the Federal Circuit (CAFC), arguing that the statute examines a drug product as a whole and not on a component-by-component basis, and therefore the combination of hydrocodone and ibuprofen was an active ingredient within the meaning of §156. However, the CAFC confirmed that the statutory language requires a drug product patent's eligibility for extension on a “component-by-component, or an ingredient-by-ingredient basis”. This was supported by the final phrase in subsection 156 (f): “including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient”. Thus, the statute referred to a drug product on a “component-by-component basis, not as a whole”. Particularly, the court noted that the disjunctive was used to show that the drug product may consist of either a single active ingredient or an active ingredient in combination with another active ingredient, placing “a drug product with two active ingredients, A and B, in the same category as a drug product with a single active ingredient. In both instances, those active ingredients individually qualify for examination under the first permitted marketing requirement.” Furthermore, Section 1 of Title 1 of the United States Code provides some general guidance for the meaning of the Code, including “words importing the singular include and

apply to several persons, parties, or things.” This general guidance, however, includes in the same section the following exception, “unless the context indicates otherwise.” In this case, the court found that the context of §156 does not permit the singular term “active ingredient” to embrace the plural.

In addition, although the FDA apparently evaluates combination drugs as a whole in determining their safety and efficacy, the Hatch-Waxman Act permits patent term extension only with regard to the active ingredient of the drug product that receives FDA approval. The CAFC rejected the view that ‘product’ should refer to the particular drug product that the FDA approved, and not a single active ingredient. This interpretation could have been suggested by the term ‘approved product’ of §156(c), and also because the FDA treats combination drugs as NDAs when evaluating their safety and efficacy. However, due to the “unambiguous language in the remainder of the section”, the term ‘product’ as defined by §156(f) has a different meaning and does not have to be in harmony with the product approved by the FDA. The court conceded that the reading of §156 does not “perfectly overlay” with FDA’s practices and regulations, which treats FDCs as new drug entities. However, since the Patent Act and the Food, Drug, and Cosmetic Act do not exhibit a perfect overlap of policies and protections, §156 would not need to supply the same term protections for combination drugs as for non-combination drugs.

The CAFC also addressed briefly whether synergistic combination drug patents qualify for a patent term extension under §156. The '252 patent at issue states:

“The combination [of hydrocodone and ibuprofen] provides an analgesic effect greater than that obtained by increasing the dose of either constituent administered alone. The adverse effects produced by such combination are considered to be less than those produced by an equi-analgesic dose of one of the constituents.”

However, the CAFC

“..doubts that synergistic effects are an appropriate distinction for term extension policies, particularly where the statutory language does not distinguish at all between synergistic and nonsynergistic combinations.”

Although a synergistic effect and a reduction of adverse side effects was disclosed in the patent, the court considered the phenomenon of synergism not suitable as a criterion for evaluating the eligibility of a FDC patent term restoration.

Interestingly, the CAFC affirmed the District Courts view which was not “not unsympathetic” towards the argument that the denial of a PTE creates a financial disincentive to the development of new therapeutic drugs. Nonetheless, the courts must decide on the basis of the statute law, whereas the matter to create a “better balanced policy” has to be addressed by Congress. Also, the court did not find the statutory history, as reviewed in *Fisons v. Quigg*⁵², to contradict the straightforward reading of the statute,

particularly none that would qualify as a “most extraordinary showing” to “justify a limitation on the ‘plain meaning’ of the statutory language.”⁵³ The legislative history of the Hatch-Waxman Act, as reviewed in the case *Fisons v. Quigg*⁵⁴ on a new medical indication, shall be discussed in the following section.

2.4 FISONS V. QUIGG – A PTE FOR A NEW MEDICAL INDICATION?

The U.K. pharmaceutical company Fisonsplc had applied for a PTE for “Opticrom 4%”, an aqueous solution of cromolyn sodium for the treatment of allergic diseases of the eye. Clinical testing and an additional three years of FDA review had reduced the effective patent life by eight years. PTO Commissioner Quigg however denied the application on the grounds that the active ingredient had already received market approval for treatment of exercise-induced bronchospasm. Undertaking an exhaustive review⁵⁵ of the legislative history of §156, the District court found that the House Energy and Commerce Committee Report accompanying H.R. 3605 had cautiously stated that Title II of the Act was intended “to create a new incentive for increased expenditures for research and development of certain products which are subject to premarket government approval [Emph. added].”⁵⁶ Specifically, restoration of patent life seemed to have been limited to ‘pioneer’ drugs. A report by the Congressional Office of Technology Assessment to the 97th Congress⁵⁷ provided the factual foundation for the restriction of patent restoration benefits to new chemical entities:⁵⁸ “Although important pharmaceutical innovations may result from new therapeutic applications of existing chemicals ... many of the pharmaceutical breakthroughs that have occurred have resulted from NCE (new chemical entity) research and the development of NCEs generally has required more time and money than other types of innovation and has involved greater risks.”⁵⁹ The House Committee on Energy and Commerce explained that the bill “requires extensions to be based on the first approval of the product because the only evidence available to Congress showing that patent time has been lost is data on so-called class I, new chemical entity drugs.”⁶⁰ The District court noted⁶¹ that some members of Congress questioned the necessity to encourage research and development even for NCEs. One argument put forward was that spurring additional research and development on drugs would not be necessary because the number of NCEs approved has remained relatively constant since 1963⁶². Others cast doubt on the proposition that drug innovation is declining, and expressed concern over monopolization created by drug patents⁶³. In *Fisons v. Quigg*, the District court found that Congress’ intent was to restore patent life only to NCEs, which is reflected directly in the restrictive definition of ‘product’ in §156(f) for purposes of §156 as the drug’s active ingredient. However, the court noted that the proposal leading to Section §156 was heavily criticized for not extending patent restoration to more types of patented products, particularly patents covering new dosages and indications. The pharmaceutical industry, in particular, criticized that the bill “does not apply to new uses for the drug, new dosage forms or innovative formulations, all of which require full new drug applications. Those innovations frequently are as important and contribute as much to public health as the active ingredients covered under the provision.”⁶⁴ Furthermore, the proposed bill “would limit unduly the

kinds of drugs and patents that would benefit from patent term restoration [...]: products with multiple patents [and] significant improvements to existing patents” would not be covered.⁶⁵ This result is accomplished through detailed and complicated restrictions on the types of patents eligible for restoration”.⁶⁶ The President of the pharmaceutical company American Home Products, John R. Stafford, described in detail the case of the beta blocker Blocadren (Timolol), which precisely addressed the complaint raised by Fisons, i.e. that new indications were not covered by the Act. Merck had obtained a patent on the compound Blocadren in 1972, and although it was approved and widely used in Europe, it only received marketing approval in the US in 1981 with only 8 years of patent life left. Merck had continued its research on the compound long after it had received approval in Europe as a cardiovascular drug, and had obtained market authorization for a new use in 1978. Specifically, Merck had discovered that the compound decreased intraocular pressure on the eye when used in eye drop form could be used very effectively for the treatment of glaucoma. Blocadren was marketed as eye drops under the name Timoptic and was considered a breakthrough drug, which in many cases eliminated the need for surgery. However, under the proposed bill, “[since] the Timoptic active ingredient was claimed in the earlier issued patent for Blocadren, it would not be entitled to patent term restoration under subparagraph (4)(A) of section 201 of the bill. On the other hand, Blocadren was not approved until 1981 while Timoptic was approved in 1978. Therefore, subparagraph (7)(A) of section 201 prevents the discoverer from getting restoration on Blocadren because Timoptic was approved first.”⁶⁷ In *Fisons v. Quigg*, the District court noted that the detailed example on the drug Blocadren was “remarkably identical” to the situation the plaintiff had complained about. However, it inferred that by “enacting and not amending Section 156 in this regard, Congress implicitly, but clearly, rejected the industry’s plea for loosened eligibility requirements.”⁶⁸ Also, the court found particularly noteworthy that Congress did not give in to the dissatisfaction communicated by the PTO Commissioner in 1984, Gerald J. Mossinghoff, to both the House and the Senate. He criticized that the bills as written did not reward investors who developed new uses for their already patented products.⁶⁹ Dissatisfaction was also expressed by patent law practitioners. For instance, the Patent, Trademark, and Copyright Law Division of the District of Columbia Bar criticized H.R. 3605’s eligibility provisions for not adopting definitions consistent with general patent law, in which each patent defines a separate and distinct invention.⁷⁰ Also, several members of Congress put forward their criticism in a letter to Representative Peter W. Rodino, Jr., Chair of the House Judiciary Committee, charging that H.R. 3605 “would discriminate against companies which innovate in areas such a new dosage forms, new delivery systems, and creative formulations ... For instance, an innovative dosage form to lessen side effects would be unprotected. Drug product innovations should receive the same protection as new chemical identities.”⁷¹ Furthermore, Representative Bliley called the patent restoration provisions of H.R. 3605 “so restrictive that their effect may well be largely illusory.”⁷² Furthermore, he commented: “the bill falls well short of providing the incentives for innovation that it purports to achieve. It is not necessary, of course, that every patent be eligible for extension in order for reasonable incentives to

innovate to exist. Rather, the bill should provide for patent term restoration for all significant innovations, be they in discovering new chemical entities, new dosage forms, new uses or species of substances previously covered by broad genus patents.”⁷³ Despite the abundant criticism, the House rejected a proposed amendment brought forward by thirteen Representatives that sought to alleviate the criticized shortcomings of the proposed bill.⁷⁴ The amendment's sponsor, Representative William J. Hughes, stated:

“Present practice provides that when you file a patent it's usually for one of three different types of patent: a patent on a product which is the most valuable, a patent for a particular type of use and/or a patent for the process by which something is made ... What usually happens is that a person receives a patent on the product and a patent on a particular use of that product. Later a new use is discovered and a new patent obtained. Under H.R. 3605 you cannot receive an extension on the new use discovered but only on the earliest issued patent. This will discourage research and innovation.”⁷⁵

The amendment, although supported by the Department of Commerce, by the Patent and Trademark Office, American Intellectual Property Law Association, and several bar groups⁷⁶, was rejected by the Judiciary Committee.⁷⁷ The Committee report explained that the amendment was defeated because the “only patented product which experiences any substantial regulatory delay is the first product patent ... Therefore, ... subsequent patents on approved drug products are frequently not the same magnitude or innovation as occurs with respect to the initial patent.”⁷⁸ The Committee concluded that “on public policy and health policy grounds ... only the first patent on a drug-type product should be extended.”⁷⁹ The legislative history quite clearly indicates that Congress intended that patent term restoration was limited to NCEs. Therefore, the District court rejected Fisons policy argument and denied patent term restoration for a new medical indication. On appeal, this decision was confirmed by the CAFC.⁸⁰

2.5 A PTE APPLICATION FOR A SYNERGISTIC FDC (“SYMBICORT”)

The most recent case concerning a PTE application for an FDC was that of AstraZeneca’s combination drug product Symbicort in 2008.⁸¹ AstraZeneca's U.S. Patent No. 5,674,860 (“the '860 patent”) claimed a combination drug product for the treatment of chronic airway diseases which has been marketed worldwide as Symbicort. Although the active ingredients formoterolfumaratedihydrate, a long-acting beta2-agonist bronchodilator, and budesonide, an anti-inflammatory corticosteroid, were both approved as separate agents before, Symbicort was the first FDC of the two active ingredients on the market. The Swedish inventors had first filed their application in 1991, and the US counterpart, the '860 patent, issued in 1997. Marketing approval by the FDA, however, was granted in the year 2006, which resulted in a long development time of approximately 15 years. The PTO, however, denied the request for a PTE. Although the combination product Symbicort was new to the market, the PTO asserted in analogy to *Arnold v. Dudas* that the first commercial marketing requirement was not satisfied. AstraZeneca, however, argued

that the combination of the two active ingredients had an unexpected synergistic effect. In its application for patent term extension, evidence was submitted for a more than additive action of the formoterol-budesonide combination from the two landmark studies 716 and 717, which formed the basis of the FDA approval.⁸² In these studies, the peak expiratory flow (PEF), a parameter for lung function, was measured for asthma patients with mild to moderate symptoms in one group (study 716), and moderate to severe symptoms in another group (study 717), as demonstrated in Figure 1, page 4 of AstraZeneca's PTE application:

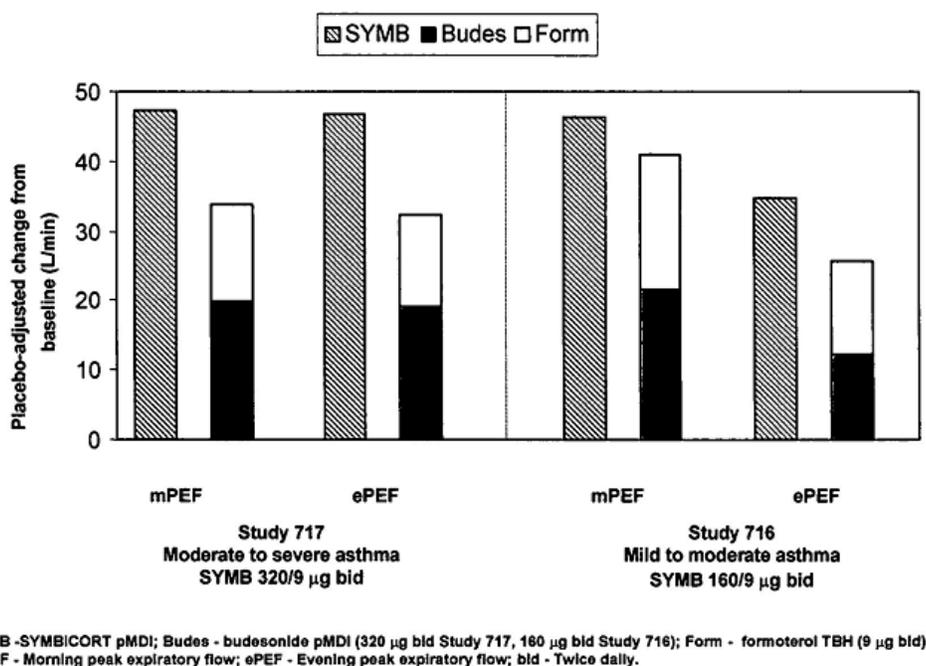


Figure 1: Morning and evening PEF: Placebo adjusted change from baseline to the average during double-blind treatment (studies 717 and 716) Taken from: Figure 1, page 4, Application for extension of patent term under 35 U.S.C. § 156 for U.S. Patent No. 5,674,860, AstraZeneca AB, Sept. 19, 2006, available online at <http://portal.PTO.gov/external/portal/pair>

AstraZeneca argued that both studies showed that the PEF is greater for Symbicort than the sum of the monoactive substances alone. Particularly the data for the group with moderate to severe asthma symptoms (study 717), depicted in Table 3, page 9 of Exhibit D of the PTE application, demonstrates that the combined PEF values for budesonide and formoterol were significantly less (approx. 30%) compared to the budesonide-formoterol combination. Similarly, a significant effect was observed for the patient group with mild to moderate symptoms⁸³, although the differences were less pronounced. Furthermore, AstraZeneca's claim for synergistic drug action was further supported by an Affidavit (Exhibit F) filed by one of the co-inventors to demonstrate non-obviousness during patent prosecution. Thereby, the declaration showed a statistically significant synergistic action of the budesonide-formoterol combination

in a sephadex-induced edema model in rats. In addition, AstraZeneca asserted that the combination of formoterol and budesonide did not show the usually occurring development of tolerance within the first few weeks of treatment and thus, a decrease of the initial beneficial effect in patients.⁸⁴ Therefore, Symbicort should be treated as one single active ingredient for the purpose of patent term extension under §156.

	Placebo adjusted change from baseline (L/min) ^a	
	LS mean (SEM)	95% CI
Morning PEF		
SYMBICORT	47.42 (4.16)	(39.24, 55.60)
Budesonide	19.95 (4.26)	(11.57, 28.33)
Formoterol	13.85 (4.19)	(5.62, 22.08)
Evening PEF		
SYMBICORT	46.84 (4.29)	(38.41, 55.27)
Budesonide	19.02 (4.40)	(10.38, 27.66)
Formoterol	13.37 (4.31)	(4.91, 21.83)

^aChange from the baseline to the average during double-blind treatment for each treatment (SYMBICORT, budesonide, and formoterol) v. placebo

Doses administered: SYMBICORT pMDI 320/9 µg bid; budesonide pMDI 320 µg bid; and formoterol TBH 9 µg bid. From Table 54 of the CSR for Study 717

Table 1: Morning and evening PEF: Placebo adjusted change from baseline to the average during double-blind treatment (study 717). Taken from: Table 3, page 9, Exhibit D, Application for extension of patent term under 35 U.S.C. § 156 for U.S. Patent No. 5,674,860, AstraZeneca, Sept. 19, 2006, available online at <http://portal.PTO.gov/external/portal/pair>

Interestingly, Astra also asserted that the Manual of Patent Examining Procedure (MPEP), which describes the application of the laws and regulations in the examination of patent applications, includes the statement in Section 2751 that “an approved product having two active ingredients, which are not shown to have a synergistic effect or have pharmacological interaction, will not be considered to have a single active ingredient made of the two active ingredients.”⁸⁵ The negative implication of this statement would be that two active ingredients showing synergism could be regarded as a single active ingredient. The

PTO, however, rejected this argument: "The statement in the MPEP does not require that the PTO treat an alleged synergistic combination drug product with two active ingredients as a single active ingredient made up of the two active ingredients for patent term extension purposes. Rather, MPEP § 2751. merely explains that a product having two active ingredients, without synergy, will not be treated as a single active ingredient." Therefore, a demonstration of synergy does not imply that the combination of active ingredients is considered asingle active ingredient for the purpose of obtaining a PTE. The PTO followed the Arnold v. Dudasdecision and denied a PTE for Symbicort.⁸⁶

3. STATUTE LAW AND CASE LAW IN THE EU

3.1 THE DEFINITION OF 'PRODUCT' IN EU REGULATION 1768/92

In the EU, Regulation 1768/92 (now codified as Regulation 469/2009) coordinated the two separate legal fields patent law and the law relating to regulatory drug approval. Thereby, an SPC grants to its owner the same rights as conferred by a patent, however with the important restriction that protection is granted only in regard to the 'product' for which marketing authorization⁸⁷ for a medicinal product has been obtained. This is one of the corner stones of the Regulation and is provided for in Article 2 therein:

"Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorization ... may, under the terms and conditions provided for in this Regulation, be the subject of a certificate. [Emph. added]"

Furthermore, Article 3 of the Regulation provides the conditions that must be met for obtaining a SPC:

"A certificate shall be granted if, in the Member State in which the application ... is submitted and at the date of that application:

(a) the product is protected by a basic patent in force;

(b) a valid authorization to place the product on the market as a medicinal product has been granted in accordance with Directive 65/65/EEC⁸⁸ or Directive 81/851/EEC⁸⁹, as appropriate; ...

(c) the product has not already been the subject of a certificate;

(d) the authorization referred to in (b) is the first authorization to place the product on the market as a medicinal product."

Particularly, the definition of the term 'product' is of central importance to determine the eligibility for a SPC, and has been reviewed by Katzka (2008).⁹⁰ The terms 'medicinal product' and 'product' are defined in Article 1 of the Regulation:

"(a) 'medicinal product' means any substance or combination of substances presented for treating or preventing disease in human beings or animals and any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in humans or in animals;

(b) 'product' means the active ingredient or combination of active ingredients of a medicinal product [Emph. added]"

Thus, a 'product' is defined as 'active ingredient' or a 'combination of active ingredients' of a 'medicinal product'. The explicit mentioning that the term 'product' not only designates a single active ingredient, but extends to a combination of active ingredients is of central importance for the determination if a

'product' is eligible for an SPC. Article 3(d) requires that the marketing authorization must be the first for a product. If the term 'product' applies to the combination of active ingredients, this combination naturally must be regarded as a separate product. Thus, if we have to determine the first marketing authorization, it follows that a later approved combination of actives is a different product over the earlier approved single active ingredients. In contrast to US practice, SPC protection can therefore be obtained for a combination of known active ingredients which already have received market authorization individually before. For instance, AstraZeneca's Symbicort, which was denied a PTE in the US, was granted SPC protection in the UK with a maximum term until 2015.⁹¹

3.2 THE DEFINITION OF 'ACTIVE INGREDIENT'

A key question that follows from Article 1(b) is what exactly is included in the term 'active ingredient', since this term is not defined in Regulation 1768/92. However, according to the Orphan Drug Regulation 847/2000, 'active ingredient' designates a substance, such as a chemical compound, with pharmacological or physiological properties on which the therapeutic effect is based.⁹² This concept must be distinguished from 'excipient', which is defined as an auxiliary substance which generally is therapeutically inert and is needed for the manufacture, administration or conservation of the active ingredient. Its function is to act as a vector or carrier for the active ingredient, thereby contributing to certain properties of the product, such as its stability, galenical form or its acceptability for the patient.⁹³ In 1996, the UK Patent Office refused a SPC application for a new dry-powder aerosol formulation, a combination of the active ingredient Serevent and 1,1,1,2-tetrafluoroethane, although the drug had been marketed before as a suspension in an aerosol propellant. Also, in 1999, the question whether new formulations are eligible for SPC protection has been put to the test by the Clarithromycin case before the Federal German Patent Court in Germany. The decision dealt with an SPC application for the antibiotic clarithromycin and potassium sorbate. A market authorization had been granted for the combination in 1991, and a SPC was granted for the active ingredient clarithromycin in 1994. The court held that potassium sorbate was a preservative and not an active ingredient. Since the active substance clarithromycin had been marketed before and potassium sorbate was an excipient, the application would contravene the requirement that only one SPC could be granted per product as laid down in Article 3(c). Therefore, a new formulation, which is a combination of an active substance and with a new excipient, is not eligible for SPC protection. Similarly, the Court of Appeals in Paris denied SPC eligibility for a new combination of the beta blocker timolol and gellane gum for the treatment of glaucoma.⁹⁴ The court found that gellane gum was merely an excipient and that Article 3(d) was contravened since the active substance timolol had already received a first market authorization in 1978. Interestingly, a SPC for the same combination was granted by several European countries, among them Belgium, Finland, Ireland, Italy, Luxembourg, Norway, and Sweden, but was rejected in the U.K.

3.3 THE ECJ'S GLIADEL DECISION

In 2006, the European Court of Justice again addressed the question of what constitutes an active ingredient pursuant to Article 1(b)⁹⁵. The Massachusetts Institute of Technology (MIT) had developed and obtained a patent for the biodegradable polymeric excipient polifeprosan, which allowed for a slow and constant release of a biologically active substance. Polifeprosan was marketed in combination with the already known chemotherapeutic drug carmustine under the tradename Gliadel for the treatment of recurrent brain tumor. Carmustine is a highly toxic alkylating agent and had already been used in intravenous cancer therapy for brain tumors for a long time. However, treatment with carmustine was not able to successfully increase the survival of cancer patients to a significant extent, and could lead to the occurrence of significant side effects. Gliadel, the combination of carmustine and the biodegradable wafer polifeprosan, allowed for direct implantation at the tumor site during surgery of brain tumor patients. Thereby, it was possible to maximize the efficacy by localized and continuous sustained delivery of carmustine which is proportional to the degradation rate of the polymer, and by minimizing systemic drug exposure⁹⁶. The landmark study which was used as the basis for FDA approval showed that Gliadel significantly increased the survival of patients with recurrent glioblastomamultiforme at the six month time interval by 56% percent (compared to 36% in patients treated with placebo).⁹⁷ Gliadel was protected by MIT's European patent No. EP0260415, which in claim 8 read "composition comprising a matrix of high molecular weight ... and a biologically active substance". The patent was filed by MIT on July 29, 1987, and the first marketing approval for Gliadel was granted in Germany on August 3, 1999. MIT applied for a SPC at the German Patent Office which was denied for the reasons that carmustine had already been granted market approval before and that polifeprosan did not constitute an 'active ingredient' pursuant to the definition of the term 'product' in Article 1(b). It also ruled that a certificate for carmustine alone could not be granted as it had received marketing authorization many years ago.⁹⁸ After an unsuccessful appeal to the Federal Patent Court, MIT lodged an appeal at the Federal Supreme Court⁹⁹. There, it was found that the German text of Article 1(b) did not necessarily entail that each of the active ingredients must have a pharmacologic activity of its own. Particularly, the definition given in Article 1(b) does not mention a combination of (individual) active ingredients, but speaks of a "Wirkstoffzusammensetzung eines Arzneimittels". According to the court, the latter terminology should include a particular component of a medicinal product that arrives at its therapeutic effect only through its interaction with other components, but not individually. In this case, this particular component would not merely constitute an excipient which one would have to have knowledge about for the correct administration of a drug, but which one has to know about in order obtain the specific therapeutic effect of the active ingredient.¹⁰⁰ This interpretation would be supported by the explanatory memorandum of the EC Commission for its proposal for a regulation¹⁰¹ stating that all pharmaceutical research which may be patented, whether it concerns a new product, a new process for obtaining a new or known product, a

new application of a product or a new combination of substances containing a new or known product, must be encouraged. Therefore, the assumption could be made that the combination of a new excipient with a known active substance will be eligible for the grant of a SPC if this combination resulted in a new medicinal product in which the therapeutic effects of the active ingredient are defined and controlled by the additional substance. Importantly, this interpretation had already been adopted by some member states of the Community, since France and the United Kingdom had granted a SPC for the product Gliadel.¹⁰² The court referred two questions to the European Court of Justice for a preliminary ruling concerning the meaning of the terms ‘active ingredient’ and ‘combination of active ingredients’, and what may be encompassed within their scope of definition:

“1. Does the concept of “combination of active ingredients of a medicinal product” within the meaning of Article 1(b) of Regulation [No 1768/92] mean that the components of the combination must all be active ingredients with a therapeutic effect?”

2. Is there a “combination of active ingredients of a medicinal product” also where a combination of substances comprises two components of which one component is a known substance with a therapeutic effect for a specific indication and the other component renders possible a pharmaceutical form of the medicinal product that brings about a changed efficacy of the medicinal product for this indication (in vivo implantation with controlled release of the active ingredient to avoid toxic effects)?”

The first question directly addresses the definition of ‘active ingredient’ and whether it may include a component which does not have a therapeutic effect of its own. The second question specifically relates to the situation where a component is added to an active ingredient that specifically enhances the efficacy of the latter.

3.3.1 OPINION OF THE ADVOCATE GENERAL

The Advocate General is an independent advisor to the court and provides a comprehensive legal analysis on cases which raise a new point of law.¹⁰³ Although the Opinion of the Advocate General is not binding upon the final decision, his judgment is followed in the majority of cases.¹⁰⁴ In the case at issue, Advocate General Léger held¹⁰⁵:

“Whilst Article 1(b) of Regulation No 1768/92, as it is worded, means in principle a combination of two or more active substances, I do not think that a purely literal interpretation of that provision allows a combination comprising an active ingredient and an excipient to be disqualified from classification as a ‘product’ within the meaning of the regulation in the specific case where the excipient is necessary for the therapeutic efficacy of the active ingredient.”¹⁰⁶

Therefore, he considered that the combination of an active ingredient and an excipient is encompassed within the literal meaning of the definition of ‘product’ of Article 1(b). This interpretation should also not be contrary to the other language versions of the regulation.¹⁰⁷ Furthermore, the Regulation established a protection system “supplementary” to that granted by a basic patent. It closely links the SPC to the basic patent, which is particularly evident from Article 5 of the Regulation specifying that a certificate confers not only the same rights as conferred by the basic patent, but is also subject to the same limitations and obligations laid down by the patent.¹⁰⁸ The Advocate General found that a restrictive interpretation of the provision would not be consistent with the “broad logic” of the regulation:

“In my view, it is not sufficient to encourage research and development of new active ingredients to ensure the continuing improvement of health care. Like MIT and the Commission, (27) I consider that research into new applications for existing active ingredients should be promoted by developing auxiliary substances enabling their use or the enhancement of their pharmacological properties for a specific therapeutic indication ... this would make it possible not only to envisage new forms of administration better suited to the patient’s specific needs (28) and to increase the efficacy of medicinal combinations, but also to ensure greater safety of use by reducing undesirable effects. (29) If no such research were conducted, I believe that many patients would have to make do with treatment that was not optimal.”¹⁰⁹

Furthermore, MIT had pointed out that the available chemotherapies offered for the treatment of brain cancer were ineffective as the intravenously administered drugs are not able to pass the blood-brain barrier. Therefore, considerable effort went into the development of new techniques of administration, including biodegradable matrices such as polifeprosan. Although it had no therapeutic properties on its own, polifeprosan increased the efficacy of carmustine and decreased the toxicity significantly through its progressive dissolution. Therefore, the Advocate General considered that the combination of carmustine with polifeprosan “... gives the active ingredient entirely new properties in terms of efficacy and safety of use” and furthermore, that the “necessity of the excipient for ensuring the therapeutic efficacy of the active ingredient ... must be the determining factor in ascertaining whether a combination of these two substances is covered by ‘combination of active ingredients of a medicinal product’.” Hence, the questions of the referring court should be answered in the affirmative, and the combination of carmustine and polifeprosan should be eligible for SPC protection.

3.3.2 FINAL JUDGMENT

In its final decision, the court came to a different conclusion.¹¹⁰ It held that the expression ‘active ingredient’ is generally accepted in pharmacology not to include substances forming part of a medicinal product which do not have an effect of their own on the human or animal body.¹¹¹ The court emphasized

that point 11 of the Explanatory Memorandum to the Proposal for a Council Regulation:

“...concerns only new medicinal products. It does not involve granting a certificate for all medicinal products that are authorised to be placed on the market. Only one certificate may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new certificate.”¹¹²

Therefore, it is apparent from the memorandum that the pharmaceutical form of the medicinal product to which an excipient may contribute would not form part of the definition of ‘product’. According to the court, the term ‘product’ is to be understood as an ‘active substance’ or ‘active ingredient’ in the strict sense. Furthermore, reference should be made to Regulation 1610/96 concerning the creation of a supplementary protection certificate for plant protection products¹¹³, where in recital 4 in the preamble it is stated that innovation in the plant protection sector requires a level of protection which is equivalent to that granted to medicinal products by Regulation 1768/92. Under Article 1(8) of Regulation 1610/96, ‘product’ is defined as the active substance or combination of active substances of a plant protection product. An active substance, under Article 1(3), is defined as a substance having general or specific action against harmful organisms or on plants. In this regard, point 68 of the Explanatory Memorandum to the Proposal concerning the creation of a SPC for plant protection products¹¹⁴ deliberately calls for a stricter definition of ‘product’:

– it would not be acceptable, in view of the balance required between the interests concerned, for the total duration of protection granted by the SPC and the patent for one and the same product to be exceeded;

– that might be the case if one and the same product were able to be the subject of several successive SPCs;

– that calls for a strict definition of the product;

– if an SPC has already been granted for the active substance itself, a new SPC may not be granted for that substance, whatever changes may have been made regarding other features of the plant protection product (use of a different salt, different excipients, different presentation, etc.);

– in conclusion, it should be noted that, although one and the same substance may be the subject of several patents and several marketing authorisations in one and the same Member State, the SPC will be granted for that substance only on the basis of a single patent and a single authorisation, namely the first granted in the Member State concerned.”[Emph. added]

In addition, Article 3(2) of Regulation 1610/96 itself provides that the holder of more than one patent for the same product is not to be granted more than one SPC for that product, supporting a strict interpretation of its definition. As set out in recital 17 in the preamble to that regulation, the detailed rules in Article 3(2), in particular, are also valid for the interpretation of Article 3 of Regulation 1768/92. Therefore, the combination of a substance with a substance which does have therapeutic effects of its own cannot give rise to a ‘combination of active ingredients’ within the meaning of Article 1(b) of Regulation 1768/92.¹¹⁵ Whether a substance without any therapeutic effect of its own is necessary for the therapeutic efficacy of the active ingredient cannot, in this case, be regarded as a sufficiently precise test and would create legal uncertainty¹¹⁶ in the application of Regulation 1768/92, running counter the objective of a uniform solution at Community level and preventing a heterogenous development of national laws¹¹⁷.

3.4 AFTER THE GLIADEL DECISION

3.4.1 NEW INDICATION – YISSUM UNIVERSITY

Following the Gliadel decision, an important ruling was handed down by the ECJ concerning new indications.¹¹⁸ Yissum University held a basic patent for the second medical use of a pharmaceutical composition containing calcitriol for dermatological application. The ECJ held: “[The SPC Regulation] is to be interpreted as meaning that in a case where a basic patent protects a second medical use of an active ingredient, that use does not form an integral part of the definition of the product.” The court followed its prior ruling in *Pharmacia Italia*¹¹⁹, in which it had held that “the decisive factor for the grant of the certificate is not the intended use of the medicinal product and ... the purpose of the protection conferred by the certificate relates to any use of the product as a medicinal product without any distinction between use of the product as a medicinal product for human use and as a veterinary medicinal product”. The court had thus denied the company *Pharmacia Italia* a SPC for the active ingredient cabergolin as a human medicine, since the same active substance had received approval for veterinarian use before. Hence, SPC protection does not extend to new medical indications, another field where incremental innovation plays a key role.

3.4.2 COMBINATION OF SOMATOTROPIN AND HISTIDIN - NOVO NORDISK

In 2008, the French Court of Appeals in Paris applied the ECJ’s Gliadel ruling to a SPC application by the pharmaceutical company Novo-Nordisk for a pharmaceutical formulation of the growth hormone Somatotropin and the amino acid histidin.¹²⁰ The addition of histidin effectively stabilizes and protects the proteo-hormone against deamidation, oxidation and cleavage of peptide bonds, for which a European Patent No. EP0618807 was granted in 2002. An SPC had already been issued to the company Genentech for a process of manufacturing Somatotropin, which as a direct product of that process should encompass

the active principle. The Court of Appeals upheld the decision of the French industrial property office that the request for supplementary protection cannot be attributed since histidin was an excipient, not an active ingredient. Thus, a SPC for a new formulation of Somatotropin was denied.

3.5 PROTECTED BY A BASIC PATENT IN FORCE

For combination products it is of particular importance to define the meaning of “protected by a basic patent in force” according to Article 3(a) of Regulation 1768/92. Principally, to be eligible for a SPC, a combination can be claimed in the same patent as the NCE, since multiple SPCs can be granted on the basis of the same patent.¹²¹ Alternatively, the combination could be claimed in a subsequent patent if it complies with the general patentability criteria novelty, inventive step, and industrial applicability. However, particularly the former two requirements present potential obstacles for a filing strategy where the combination is claimed in a follow-up patent. Generally, the question arises if it is sufficient that an active ingredient A is claimed in combination with “another active ingredient”, or if the second active substance be explicitly mentioned (e.g. “A in combination with B”)?¹²² Moreover, this is taken to the extreme if the patent only protects one of the active ingredients of the combination and does not mention the combination per se. In this case, a combination comprising the protected active ingredient might infringe the patent. However, the question may be raised if infringement is sufficient to be considered as protected by a basic patent in force pursuant to Art 3(a) of the Regulation. So far, this question has been considered by the two consecutive Takeda and Gilead decisions taken by the UK High Court in 2003 and 2008, respectively.

3.5.1 TAKEDA CHEMICAL INDUSTRIES

In the Takeda case¹²³, the court had to decide whether an SPC could be granted for a combination of active ingredients, although only one active ingredient was claimed by the patent, and not the combination per se. Takeda Chemical Industries Ltd. was the owner of a patent for the proton pump inhibitor lansoprazole, for which it was granted a SPC. Additional research showed that the new compound could be effectively combined with certain other antibiotics to fight gastric ulcer, and the product license was amended to include this new indication. Takeda’s request for a SPC for the combination, however, was rejected by the Hearing Officer, who considered that only one element of the combination, lansoprazole, was claimed in the patent, and the specification neither disclosed nor suggested that the products of the invention could be used in combination with other active ingredients. Therefore, the combination was held not to be protected pursuant to Article 3(a). On appeal, the High Court found that the fact that the combination might infringe the patent is irrelevant, since “the so-called ‘combination’ of lansoprazole and an antibiotic would only infringe because of the presence of the lansoprazole. In truth, the combination is not as such ‘protected by a basic patent in force’”. Mr. Justice Jacob also made reference to the Hässle AB decision taken by the Swedish Supreme Administrative Court

on a combination of two active ingredients, where only one active principle was claimed in the patent, and not the combination per se.¹²⁴ Thus, the UK High Court ruled that not everything that infringes can be considered to be protected as such within the meaning of Article 3(a) and rejected Takeda's appeal.

3.5.2 GILEAD SCIENCES INC

In 2008, the UK High Court again considered the meaning of Article 3(a) of the Regulation in regard to combination products.¹²⁵ Gilead Sciences Inc. had applied for an SPC for a combination of the two antiretroviral compounds tenofovir and emtricitabine. Claim 1 of Gilead's patent covered a certain class of antiretroviral compounds, and claim 25 was specifically directed to tenofovir itself. In contrast to Takeda, Gilead's basic patent was also directed to the combination as such. Claim 27 read: "A pharmaceutical composition comprising a compound according to any one of claims 1-25 together with a pharmaceutically acceptable carrier and optionally other therapeutic ingredients." However, the Hearing Officer relied upon Takeda that not everything that infringes the patent is protected according to Article 3(a), and the patent specification should at least provide a 'clear pointer' in regard to the other ingredients of the combination (although the actives need not be specifically claimed). On appeal, Justice Kitchin considered Gilead's first submission that Takeda was incorrect and that the product was not only protected by claim 27 (to the combination), but also by claim 1-25 (to tenofovir alone). In regard to this particular point, J. Kitchin rejected the submission and confirmed J. Jacob's view in Takeda, since this

"would mean that the holder of a basic patent could first obtain an SPC for the active ingredient the subject of the patent, so giving him perhaps one or two years of protection beyond the life of the patent, and then, some years later, obtain another SPC for a combination of the same ingredient together with another active ingredient and so gain protection for a full five years beyond the life of the patent. That, it may be said, is contrary to the purpose of the Regulation which is to provide an effective period of protection for the invention the subject of the patent and so encourage research, and not to provide an extension of protection based upon the adoption of another, possibly quite different, ingredient."

In essence, the court rejected the idea that a monopoly can be claimed via an SPC that has no basis in the patent. Nonetheless, J. Kitchin indicated that the ECJ's *Farmitalia* decision¹²⁶ had not been "fully explored" by the Takeda ruling. There, the ECJ had held that whether a combination is protected by a basic patent pursuant to Art. 3(a) of the Regulation must be determined by national patent law, since the latter is not harmonized at a European Community level. According to J. Kitchin, the ECJ must have had in mind Art. 69 EPC (at least concerning the EPC contracting states), which governs that a product is protected as long as it falls within the scope of a claim. The interpretation according to Art 69 EPC, e.g. that a product is protected if it would infringe the patent, had, however, been rejected in Takeda for the reasoning

explained above. This leaves an open question how Art. 3(a) should be interpreted according to Farmitalia. Gilead's case, however, was different from Takeda, since combinations of tenofovir with other active ingredients were claimed in claim 27 of the patent. Moreover, J. Kitchin rejected the "clear pointer" test the Hearing Officer had derived from the Takeda decision since a disclosure requirement has no basis in the Regulation. Instead, he formulated a new test:

"Thus I believe a test emerges from Takeda which is clear and can be applied without difficulty to a product comprising a combination of active ingredients. It is to identify the active ingredients of the product which are relevant to a consideration of whether the product falls within the scope of a claim of the basic patent. It is those ingredients, and only those ingredients, which can be said to be protected within the meaning of the Regulation. So, in the case of a product consisting of a combination of ingredients A and B and a basic patent which claims A, it is only A which brings the combination within the scope of the monopoly. Hence it is A which is protected and not the combination of A and B."

The court found that the product was protected by the patent since the combination of tenofovir with another active ingredient was claimed in the patent. Importantly, in contrast to Takeda, the combination must be claimed, but not specifically disclosed in the basic patent. J. Kitchin noted, however, that this test could lead to "harsh" results under certain circumstances, for instance, when a drug manufacturer decides to market a new active ingredient only in combination with other active ingredients. If the combination is not claimed in the patent, the product would not be protected according to Art. 3(a).

4. DISCUSSION

FDCs may have significant advantages over their single drug counterparts. For instance, they are capable of providing better compliance, reduced toxicity, and increased efficacy compared to single drug treatment regimens. Moreover, a drug combination displaying unknown effects that cannot be predicted by assessing individual drug actions alone is generally considered as inventive, and may give the proprietor the full benefits of a 20-year patent protection term. Also, FDCs are generally treated as new drug products by regulatory authorities, and require extensive clinical testing which often exceeds the requirements for new drug entities, since the combination generally must be compared to each of the single drugs in regard to safety and efficacy. From this point of view it seems a relevant question to ask if FDCs that are considered as a patentable invention qualify for extension of the patent term. Innovator pharmaceutical companies depend more on patenting than any other industry sector to recoup the investment associated with the identification of NCEs and development of new drug products. Particularly, since the research-based pharmaceutical industry will lose patent protection for a significant proportion of its best selling drug products within the next few years, obtaining patent protection for incremental innovations such as FDCs, new formulations and new indications may become an even more important strategy to guarantee a constant revenue stream for financing R&D.

In the US, a restrictive approach is followed in regard to the grant of patent term extensions for FDCs with already approved active ingredients. This was demonstrated by a series of case law beginning with the PTO decision EMLA topical cream in 1994. There, the PTO rejected patent term restoration for an FDC of two local anesthetics, although it had unique properties by forming an eutectic mixture.¹²⁷ Although this effect is not synergistic per se, it allows for higher concentrations of active moieties and improves the efficacy of the final drug product. In *Arnold v. Dudas*, patent term extension was denied by the CAFC for the FDC Vicoprofen, although a synergistic action was disclosed in the patent specification. Moreover, in the *Symbicort* decision from 2008, the PTO rejected a PTE application, although a synergism could be demonstrated in clinical trials by the applicant. Importantly, the PTO rejected the argument that the relevant “product” must include both active ingredients because of a synergistic action of the combined products. The PTO relied on *Arnold v. Dudas*, where the CAFC had ruled that synergism may not be an appropriate criterion to judge for PTE eligibility. This may be a reasonable objection, particularly since the wording of the statutory language does not seem to allow for a more liberal interpretation. In addition, synergy is often difficult to assess in practice. However, if the presence of unexpected effects is considered during the patent examination procedure to overcome obviousness type objections, the question may be put forward why the same criterion used for patenting should not apply to term extension of the same patent. In a synergistic action it is inherent that the elements lose a part of their individual distinction, and therefore the combination may be viewed as a novel entity. Thus, it could be

argued that a synergistic combination may constitute a new product. This view, however, is not reflected in §156 of the US Patent Act. Moreover, the legislative history of the Hatch-Waxman Act seems to quite clearly indicate that patent term restoration has been deliberately restricted only to NCEs.

It has to be kept in mind that the initial proposal for patent term restoration in the US was met by heavy criticism from different interest groups, and when the Act was finally passed by Congress, it not only contained the initial proposal for patent term restoration, but also a new and powerful section concerning a facilitated entry of generic drugs. Although the compromise nature of the Act has been called a great achievement by many, it has also been heavily criticized for favoring one side over the other. The research intensive pharmaceutical industry on the one hand criticized that the scope of the patent term restoration was not far reaching enough, since it prima facie did not extend protection to new formulations and indications. The Congressional debates during the legislative history of the Act clearly show that the members of Congress and representatives from the pharmaceutical industry were quite aware of this restriction at that time. On the other, various interest groups voiced their concern over extending already powerful exclusionary rights much further than it was considered necessary. The accommodation of naturally opposing interests seems to be reflected in the relatively narrow scope of 35 U.S.C. §156. Therefore, extending the patent term has to be ruled out for FDCs that consist of already known compounds. For obtaining a PTE, at least one compound of the combination must be new.

Interestingly, the limitation in regard to FDCs is not as strict in the EU, since SPCs can be granted for FDCs that do not contain a new active ingredient. In the EU, the attention has rather been shifted to what constitutes an active ingredient, and the ECJ's Gliadel decision has adopted a narrow view on what can be encompassed within this definition. The ECJ's Yissum University judgment, which immediately succeeded Gliadel, also ruled out SPCs for new medical indications. This perspective is again very similar to that of the PTO and the US courts. The research-based pharmaceutical industry, however, faces significant changes, since the discovery of NCEs has become increasingly difficult, and a considerable number of blockbuster drugs will lose patent protection within the next 3 years. Revenues lost from declining sales of blockbuster drugs will have an impact on financing costly research and development processes for new medications. This seems to indicate that research may be even more shifted to improve known treatment regimens by finding new indications or new combinations for already known compounds. An overly restrictive approach to grant term extensions may present a bottleneck and will curtail the funding available for development of new therapies. Therefore, it may be asked if the profound legislative changes in regard to patent term restoration, which started 25 years ago by introduction of the Hatch-Waxman Act, are still able to provide for sufficient incentives for R&D in the medical field. Concerns seem warranted that an overly restrictive approach adds to the challenge the healthcare sector will be confronted with, and therefore, may have a negative impact on providing new and improved treatment regimens in the future. However, current case law on both sides of the Atlantic favors a broad view of

what constitutes a first marketing authorization, and thus, the provisions regarding combination drug products and other incremental innovations are generally of narrow scope. At the moment, there seems to be little prospect of legislative change.

A yet unresolved question in regard to FDCs relates to the requirement that the product for which an SPC should be obtained needs to be protected by a basic patent in force. Specifically, what exactly needs to be disclosed in the patent to warrant an extension of the patent term by an SPC? From the most recent decision from a UK court, the Gilead ruling, it follows that there must be a claim for a combination in the patent, but the other active ingredients do not have to be identified. The optimal strategy for claiming a combination, however, may be difficult to implement. On the one hand, claiming the combination in the patent for the NCE may run the risk that the claim to the combination is not specific enough to comply with Article 3(a) of the Regulation, i.e. that the combination drug product is not considered to be protected by a basic patent. On the other, claiming the combination in a subsequent patent may entail that the patentability requirements novelty and inventive step are not met. Also, the combination may be inadvertently disclosed during clinical trials at the clinical trial hospital centers, adding to the risk that the FDC would not be considered patentable anymore.

Furthermore, the Farmitalia decision did not lay out precise steps but merely refers to national patent law in regard to Art. 3(a). Since the scope of protection is governed by Art. 69 (and the Protocol to Art. 69) for EPC contracting states, it can be inferred that a test should not contradict these particular provisions. As has been laid out in Takeda and Gilead, however, mere infringement of a product should not suffice to satisfy Art. 3(a) for reasons of granting a monopoly for something that finds no basis in the patent. This contradiction can only be resolved in two ways. Either the infringement test is adopted, or a separate set of rules is followed to establish whether a product is protected by a basic patent. The Regulation, however, does not provide for these rules, which creates legal uncertainty, and possibly a need of clarification on a European level. Moreover, in Takeda another test was put forward that there must be a clear indication in regard to the identity of the other compounds in the combination for which SPC protection is sought. This created a situation where the validity of a claim is evaluated in terms of sufficiency of disclosure and validity, which however should be the subject of patent invalidity proceedings. If a patent claim does not comply with the requirements of patent law, i.e. extends beyond what is supported by the description, the claim should be invalidated in the first place. Thus, preventing extension of monopoly rights that are not based in the patent should be left to invalidity proceedings.

Taken together, it is currently unresolved how Art. 3(a) should be interpreted. A reasonable solution is indicated by the Gilead ruling, which requires that the combination is claimed in the patent, but rejects the disclosure requirement of the previous Takeda decision. To provide uniform application of the law and to avoid a conflict with Farmitalia, this matter should, however, be resolved on a Community level.

5. CONCLUSION

Incremental inventions represent an important form of innovation in the pharmaceutical field. Therefore, it is important to assess how patent term restoration regimens apply to drug products that are based on already marketed single drug compounds, as is the case for many fixed-dose combination drugs. FDCs are eligible for a 20-year term of patent protection, provided the requirements of novelty, inventive step, and industrial application are satisfied. Their eligibility for patent term extension pursuant to 35 U.S.C. §156, however, is limited in the US, since at least one of the active ingredients must not have received market approval previously. In contrast, Supplementary Protection Certificates are available for fixed-dose combination drugs in the EU, regardless whether the active ingredients have been marketed before individually. However, the definition of what constitutes an active ingredient is rather narrow, and only encompasses molecular entities that are therapeutically active individually. Moreover, the interpretation of Art. 3(a) of Regulation 1768/92, which provides that a product must be protected by a basic patent in force, has not been fully resolved on a Community level.

BIBLIOGRAPHY

- ¹ A. I. Wertheimer, A. Morisson, Combination Drugs: Innovation in Pharmacotherapy, Combination Drugs: Innovation in Pharmacotherapy. Pharmacology and Therapy, 2002, Vol. 27 (1), p.44-49
- ² Herrick, Tara M., Million, Ryan P., Tapping the potential of fixed-dose combinations, Nature Reviews Drug Discovery, 6, 513-514 (July 2007), available at <http://dx.doi.org/10.1038/nrd2334>
- ³ P.L. 98-417
- ⁴ G. Permanand, EU pharmaceutical regulation, Manchester Univ. Press, 2006, p.96
- ⁵ G. J. Mossinghoff, Overview of the Hatch-Waxman Act and its impact on the drug development process, Food and Drug Law Journal, 54(2), 1999, p. 188
- ⁶ Except for antibiotics, and under drug products already marketed before the 1962 amendment of the U.S. Federal Food, Drug, and Cosmetic Act, which had introduced the requirement for drug manufacturers to show that a drug was safe and effective
- ⁷ 21 U.S.C. §355(b)(2)(a)
- ⁸ W. H. Schacht, J. R. Thomas, Hatch-Waxman Related Provisions of the Medicare Prescription Drug Bills (H.R. 1 and S. 1): A Side-by-Side Comparison, updated September 15, 2003, CRS Report for Congress, available at <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL32003.pdf>
- ⁹ The list of “Approved Drug Products with Therapeutic Equivalence Evaluations”, commonly known as the “Orange Book”, published annually by the FDA (with monthly supplements), 29th edition available at www.fda.gov, online search (continuously updated) available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>
- ¹⁰ 35 U.S.C. §156, available at http://www.PTO.gov/web/offices/pac/mpep/documents/appxl_35_U_S_C_156.htm
- ¹¹ D. Schennen, Die Verlängerung der Patentlaufzeit für Arzneimittel im Gemeinsamen Markt, 1993, Bundesanzeiger, p.12
- ¹² amending former Directive 65/65/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products; 26 January 1965; now integrated into Directive 2001/83/EC relating to medicinal products for human use, 6 November 2001
- ¹³ H. Suchy, Patentrestlaufzeit neuer pharmazeutischer Wirkstoffe, GRUR 1987 (Jahrgang 89 Heft 5), 268
- ¹⁴ H. Suchy, Patentrestlaufzeit neuerer pharmazeutischer Wirkstoffe, GRUR 1992, 7
- ¹⁵ as cited in FN11, p.13
- ¹⁶ Proposal for a Council Regulation (EEC) concerning the creation of a supplementary protection certificate for medicinal products, COM (90) 101 final – SYN 255, 11 April 1990, point 29(2), printed in: FN11, p.100
- ¹⁷ See FN16 point 8
- ¹⁸ and not an extension of the patent per se; as a sui generis right, the SPC is separable from the patent with the effect that it could be held by a party different from the patent holder

-
- ¹⁹ Article 63 of the EPC was modified on December 17, 1991 to specify that although European patents have a term of 20 years as from the date of filing of the application (Art. 63(1)): " nothing (...) shall limit the right of a Contracting State to extend the term of a European patent, or to grant corresponding protection which follows immediately on expiry of the term of the patent, under the same conditions as those applying to national patents: ... (b) if the subject-matter of the European patent is a product or a process of manufacturing a product or a use of a product which has to undergo an administrative authorisation procedure required by law before it can be put on the market in that State."
- ²⁰ AHP Manufacturing, ECJ, C-482/07, 3 September 2009
- ²¹ Regulation 1768/92/EEC concerning the creation of a supplementary protection certificate for medicinal products, 18 June 1992; Regulation 1768/92 has recently been replaced by codified Regulation EC Regulation 469/2009 from 6 May 2009; available at <http://eur-lex.europa.eu>
- ²² Farmitalia, ECJ, C-392/97, 16 September 1999
- ²³ P. R. Thomsen, Erteilungspraxis von Ergänzenden Schutzzertifikaten in Deutschland, Unter besonderer Berücksichtigung der sogenannten Salzproblematik, Berkeley Electronic Press, 2000
- ²⁴ See FN36
- ²⁵ M. Schafer-Korting and H. C. Korting (Eds.), The Benefit/Risk Ratio: A Handbook for the Rational Use of Potentially Hazardous Drugs (1998), Informa Healthcare, Chapter 5: P. Thürmann, J. Hasford, Establishing the Benefit/Risk Ratio with Combination drugs, p.79
- ²⁶ Herrick, Tara M., Million, Ryan P., Tapping the potential of fixed-dose combinations, Nature Reviews Drug Discovery, 6, 513-514 (July 2007), available at <http://dx.doi.org/10.1038/nrd2334>
- ²⁷ Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, Department of Health and Human Services, 3 November 2008; 1-139, available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
- ²⁸ B. Julg and J. Bogner, Atripla – HIV therapy in one pill, Therapeutics and Clinical Risk Management, 2008 June, 4(3), p.573–577
- ²⁹ Gilead’s two-drug fixed-dose product Truvada was the highest selling antiretroviral drug with global sales of 2100 \$m in 2008, closely followed by Atripla (1500 \$m), company financial results available at <http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-earnings>
- ³⁰ Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (EPR–2 1997), NIH Publication No. 97-4051, National Heart, Lung, and Blood Institute, http://www.nhlbi.nih.gov/guidelines/archives/epr-2/asthgdln_archive.pdf
- ³¹ K. F. Rabe et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study, Lancet, 2006; 368: p.744-53
- ³² Annual Report, GlaxoSmithKline plc, average annual exchange rate £/US\$=1.85, <http://www.gsk.com/investors/index.htm>
- ³³ H. S. Nelson et al. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. J. Allergy Clin. Immunology 112, 29–36 (2003)
- ³⁴ Annual Report 2008, AstraZeneca, available at <http://www.astrazeneca-annualreports.com/2008/>

-
- ³⁵ The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National Institutes of Health, National Heart, Lung, and Blood Institute, 2004, available at <http://www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.htm>
- ³⁶ See FN1
- ³⁷ as cited in FN36, p.44: W. H. Frishman et al, First-line therapy option with low-dose bisoprololfumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J ClinPharmacol*, 1995, 35(2), p.182-188; S. J. Guul et al., The efficacy and tolerability of enalapril in a formulation with a very low dose of hydrochlorothiazide in hypertensive patients resistant to enalaprilmonotherapy, *Am J Hypertension*, 1995, 8(7), p.727-731
- ³⁸ as cited in FN36, p.44: J. Chalmers, Efficacy and acceptability of the fixed low-dose perindopril-indapamide combination as first-line therapy in hypertension. *Eur Heart J Supplements*, 1999, 1(Suppl L):L20-L25; S. G. Chrysanter al., Effects of benazepril and hydrochlorothiazide, given alone and in low- and high-dose combinations, on blood pressure in patients with hypertension, *Arch Fam Med*. 1996; 5(1):17-24
- ³⁹ Novartis Annual Report 2008, available at http://ir2.flife.de/data/novartis/igb_html/index.php?bericht_id=1000001&lang=ENG
- ⁴⁰ PTO, Final Determination, March 3 1994, FDA Docket No. 93E-0130, available at http://www.regulations.gov/03-03-1994_Final_Determination
- ⁴¹ abbreviation for “Eutectic Mixture of Local Anesthetic”
- ⁴² See FN40 p.3
- ⁴³ See FN40 p.3
- ⁴⁴ See FN40 p.2
- ⁴⁵ See FN40 p.5
- ⁴⁶ FDA Staff Manual Guide No. CDER 4820.3 dated January 22, 1992
- ⁴⁷ *Arnold Partnership v. Dudas*, 362 F.3d 1338 (24 March 2004) Rader, J.
- ⁴⁸ No commercial break for combination treatment, *Nature Reviews Drug Discovery* (3) p.380 (2004), available at <http://dx.doi.org/10.1038/nrd1390>
- ⁴⁹ PTO, Final Determination, Nov 20,2001, FDA Docket No. 98E-0792, available at <http://www.PTO.gov>
- ⁵⁰ 5 U.S.C. Subchapter II, available at <http://www.archives.gov/federal-register/laws/administrative-procedure/>
- ⁵¹ *Arnold Partnership v. Rogan*, Eastern District Court of Virginia, 246 F. Supp. 2d 460 (2003)
- ⁵² *Fisons v. Quigg*, United States Court of Appeals for the Federal Circuit, 57 USLW 2708; 10 U.S.P.Q.2d 1869; 876 F.2d 99, 16 May 1989
- ⁵³ *Garcia v. United States*, 469 U.S. 70, 75 (1984)
- ⁵⁴ *Fisons v. Quigg*, United States Court of Appeals for the Federal Circuit, 57 USLW 2708; 10 U.S.P.Q.2d 1869; 876 F.2d 99, 16 May 1989
- ⁵⁵ See FN54 p.8, in FN3 therein it was noted that “The parties have submitted four volumes of House and Senate reports, hearings, and floor debates as part of the Administrative Record.”

-
- ⁵⁶ H.R.Rep. No. 98-857, supra note 30, at 15 [AR at 0355] (emphasis added), as cited in FN54 p.5
- ⁵⁷ H.R.Rep. No. 97-696, supra note 29, at 6 [AR at 0323] (the OTA report was commissioned by the Subcommittee on Courts, Civil Liberties, and the Administration of Justice in the First Session of the 97th Congress), as cited in FN54 p.6
- ⁵⁸ See also numerous scholarly articles reprinted Hearings on H.R. 3605, supra note 1, at 1206-93 [SLM at 027-114], as cited in FN54 p.6
- ⁵⁹ H.R.Rep. No. 97-696, supra note 29, at 6 [AR at 0323], as cited in FN54 p.6
- ⁶⁰ H.R.Rep. No. 98-857, supra note 30, at 38 [AR at 0378] (emphasis added), as cited in FN54 p.6
- ⁶¹ FN54, cited in FN47 therein
- ⁶² H.R.Rep. No. 97-696, supra note 29, at 22 [AR at 0339] (Dissenting Remarks of Rep. Frank), as cited in FN54
- ⁶³ S.Rep. No. 97-138, supra note 29, at 21 [SLM at 135] (Additional View of Sens. Kennedy and Metzenbaum), as cited in FN54
- ⁶⁴ Hearings on S. 2748, supra note 29, at 108 [AR at 0174], remarks of V. Willaman on behalf of 10 leading pharmaceutical companies, as cited in FN54
- ⁶⁵ See FN64 at 128 [AR at 0194]
- ⁶⁶ See FN64 at 135 [AR at 0201]
- ⁶⁷ See FN64 at 138-40 [AR at 0204-06] (reprinting Stafford's comments submitted on H.R. 3605 before the House Judiciary Committee on H.R. 3605 [AR at 0287-89])
- ⁶⁸ See FN54 p.7
- ⁶⁹ See FN64 at 158 [AR at 0224]
- ⁷⁰ Hearings on H. 3605, supra note 1, at 816 [SLM at 024], cited in "Any technological development may have within it several patentable aspects, each of which would support a patent. For example, a product is patentable separately from the method of making the product. They are separately patentable because the patent law treats each as a separate invention.... This bill, however, draws distinctions based, in part, upon separate inventions disclosed in earlier issued patents. The law governing this aspect of patent law is complex and the subtle distinctions which this bill attempts to draw to deny extension to certain patents will be difficult at best to implement." As cited in FN54 p.13, FN52 therein
- ⁷¹ See FN70 at 764 [AR at 0317]
- ⁷² H.R.Rep. No. 98-857, supra note 30, at 75 [AR at 0414] (Minority Views of Rep. Bliley)
- ⁷³ See FN72 at 76 [AR at 0416] (emphasis added)
- ⁷⁴ See FN54 p.7
- ⁷⁵ See FN72 note 39
- ⁷⁶ See FN75 at 58-59 [AR at 0474-75] (Additional Views of Rep. Hughes)
- ⁷⁷ See FN75 at 7 [AR at 0423]

78 See FN75 at 8 [AR at 0424]

79 See FN78

80 See FN54

81 as of August 2009

82 Application for extension of patent term under 35 U.S.C. § 156, U.S. Patent No. 5,674,860, Sept. 19, 2006, AstraZeneca AB, available at <http://portal.PTO.gov/external/portal/pair>

83 Study 716 from Table 4, page 9 of Exhibit D, see FN82

84 Figure 2 on page 10 of Exhibit D shows that the addition of budesonide to formoterol eliminates the development of tolerance in the moderate to severe asthmatic patient group over the observed time period of 12 weeks. According to AstraZeneca, a similar beneficial effect was also claimed for the patient group with mild to moderate asthma symptoms. See FN82.

85 MPEP 2751, available at http://www.PTO.gov/web/offices/pac/mpep/documents/2700_2751.htm#sect2751

86 Interestingly, as an alternative reason for the rejection of the PTE application, the PTO found that AstraZeneca had missed the sixty-day period required for filing the request for patent term restoration by one day, which was thus rendered ineligible.

87 pursuant to Directive 2001/83/EC relating to medicinal products for human use, 6 November 2001, or centrally under Regulation 726/2004/EC laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 31 March 2004, available at <http://eur-lex.europa.eu>

88 See FN12

89 Council Directive 81/851/EEC on the approximation of the laws of the member states relating to veterinary medicinal products, 28 September 1981, available at <http://eur-lex.europa.eu>

90 C. Katzka, Interpretation of the term ‘product’ in EU Council Regulations 1768/92 and 1610/96 on Supplementary Protection Certificates, *Journal of Intellectual Property Law & Practice*, 5 August 2008

91 UK Patent Office, SPC/GB02/033. In 2007, however, European Patent No. EP0613371 that served as a basis for the SPC was revoked by the EPO in an appeal to an opposition proceeding.

92 Article 3(3)(a): “... (a) ‘active substance’ means a substance with physiological or pharmacological activity” of Regulation 847/2000/EC laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product, 27 April 2000, available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:103:0005:0008:EN:PDF>

93 defined in the reference list of the European Pharmacopoeia, available at <http://www.edqm.eu>, as cited in FN105 at point 11

94 Merck & Co v. INPI, *Courd’Appel de Paris*, 4^{ème} Chambre, 6 November 2002

95 Massachusetts Institute of Technology, E CJ, C-431/04, 4 May 2006, available at <http://curia.europa.eu>

96 R. Williams, D. Taft, J. McConville (Eds.), *Advanced Drug Formulation Design to Optimize Therapeutic Outcomes*, Chapter 6 (D. Taft and X. Yuan): *Strategies for Delivery of Cancer Chemotherapy*, in: *Drugs and the Pharmaceutical Sciences*, 2007, Informa Healthcare, Vol. 172, p. 199

-
- ⁹⁷ H. Brem et al, Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group, *The Lancet*, Vol. 345, No. 8956, p. 1008-1012
- ⁹⁸ the first authorisation to place carmustine on the market was granted on 6 March 1979 in the United Kingdom
- ⁹⁹ BGH, X ZB 5/03, 29 June 2004, available at <http://www.bundesgerichtshof.de>
- ¹⁰⁰ See FN 99, paragraph 2(d), p. 11
- ¹⁰¹ See FN16 point 29(2)
- ¹⁰² Gliadel has been granted SPC protection in France (granted 7 July 2000) and in the United Kingdom (granted as SPC/GB01/013 on 16 January 2003 with a maximum period expiring on 28 July 2012)
- ¹⁰³ “...reasoned submissions on cases which, in accordance with the Statute of the Court of Justice, require his involvement.”, Article 222, Consolidated Version of the Treaty establishing the European Community, Official Journal C 325, 24 December 2002, based on the Treaty establishing the European Economic Community (Treaty of Rome), effective 1 January 1958, available at <http://eur-lex.europa.eu/en/treaties/index.htm>
- ¹⁰⁴ “Despite its non-binding nature, the Opinion of the Advocate General have considerable weight on account of the high-weight legal analysis which they contain and they are frequently cited in the Court and in writing as persuasive sources of authority. The opinion is fully reasoned ... In the vast majority of cases, the judgment of the courts will follow the opinion”, J. Fairhurst, *Law of the European Union*, part 1 chapter 5, p. 160, 2007, Pearson Education
- ¹⁰⁵ Opinion of Advocate General Léger, Massachusetts Institute of Technology, ECJ, C-431/04, 24 November 2005
- ¹⁰⁶ See FN105 point 38
- ¹⁰⁷ FN105, at FN22 therein, “None of the other language versions of the regulation dispels my doubts as to the interpretation of that provision. The versions, including the French (‘composition de principes actifs d’un médicament’), German (‘Wirkstoffzusammensetzung eines Arzneimittels’), Spanish (‘composición de principios activos de un medicamento’), Italian (‘composizione di principi attivi di un medicinale’), and Dutch (‘samenstelling van werkzame stoffen van een geneesmiddel’) are similar to the English version.”
- ¹⁰⁸ See FN105 point 40
- ¹⁰⁹ See FN105 point 48
- ¹¹⁰ Massachusetts Institute of Technology, ECJ, C-431/04, 24 November 2005
- ¹¹¹ See FN110 point 18
- ¹¹² See FN101, printed in FN11, p.95
- ¹¹³ Regulation (EC) No 1610/96 of the European Parliament and of the Council concerning the creation of a supplementary protection certificate for plant protection products, 23 July 1996, OJ 1996 L 198, p. 30
- ¹¹⁴ Proposal for a European Parliament and Council Regulation (EC) concerning the creation of a supplementary protection certificate for plant protection products, 9 December 1994, COM(94) 579 final, as cited in FN110 point 23
- ¹¹⁵ See FN110 point 26

-
- ¹¹⁶ See FN110 point 29
- ¹¹⁷ See FN110 point 30
- ¹¹⁸ Yissum R&D Company of the Hebrew University of Jerusalem v. Comptroller-General of Patents, E CJ, C-202/05, 17 April 2007
- ¹¹⁹ Pharmacia Italia, E CJ, C-31/03, paragraph 20, 19. October 2004
- ¹²⁰ Novo Nordisk, v. INPI, Cour d'Appel de Paris, 4^{ème} Chambre, 11 April 2008, published in PIBD 2008, 876, III, p. 355
- ¹²¹ This strategy may bear the advantage that if the marketing approval for the combination was at a later date than the NCE and within the maximum 15-year protection term, a longer effective patent term could be obtained for the combination
- ¹²² J. Dietz, P. R. Thomsen, presentation at MASIP, ETH Zurich, Switzerland, 25 March 2009
- ¹²³ Takeda, England and Wales High Court, 2003 EWHC 649(Pat), 2 April 2003
- ¹²⁴ Hässle AB, Swedish Administrative Supreme Court, Case No. 3248-1996, 2 February 2000
- ¹²⁵ Gilead, England and Wales High Court, 2008 EWHC 1902 (Pat), 31 July 2008
- ¹²⁶ See FN22
- ¹²⁷ The preparation of eutectic mixtures is a generally known principle for formulating poorly soluble drugs. The active ingredient is mixed with a highly soluble carrier at such proportions that the obtained mixture dissolves more easily than the solid single components due to the microcrystalline properties of the combination. Described in: A. Florence, T. Attwood, Physicochemical Principles of Pharmacy, 4th Ed, Pharmaceutical Press 2006, p.28