New Dosage Forms of Old Substances

– Regulatory Strategies and Challenges in the European Union –

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Dr. med. David Thalmann

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Erstgutachterin: Dr. Birka Lehmann

Zweitgutachter: Prof. Dr. Karl Wagner

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List of Abbreviations

BE	Bioequivalence
CE	Conformité Européenne
DE	Data Exclusivity
EDQM	European Directorate for the Quality of Medicines & HealthCare
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GMA	Global Marketing Authorisation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Inc.	Incorporated
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAD	Nasal Intranasal Mucosal Atomization Device
MAH	Marketing Authorisation Holder
mg	Milligram
mL	Millilitres
MP	Market Protection
NtA	Notice to Applicants
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PUMA	Paediatric Use Marketing Authorisation
R&D	Research and Development
RMP	Reference Medicinal Product
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate

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1 Introduction, Problem Statement & Aim of the Thesis

1.1 Introduction

Each year more than 30 billion Euro are spent for pharmaceutical research and development (R&D) in the European Union (EU) [1]. This reflects the enormous innovative potential of the pharmaceutical industry. In the light of these significant expenditures it does not seem to be surprising that the European Medicines Agency (EMA) annually issues around 30 to 40 positive opinions for new active substances [2–4]. A majority of these new substances is related to the field of oncology. Considering costs of around 650 million US-Dollar for the development of a single oncologic substance [5] and taking into account the relatively high number of new active substances entering the European market each year, it can be assumed that also a significant part of the total European R&D budget is dedicated to the development of new substances. Consequently, the shareholders' expectations of the pharmaceutical companies to actually achieve a marketing authorisation are substantial. Reports about successful or failed authorisations of new active substances often directly impact the share price of large pharmaceutical companies. Sometimes these reports even make it into the lay press.

However, there is a nondescript much less prestigious type of pharmaceutical innovation which is nevertheless important. It is the development of new pharmaceutical forms of known active substances. It is often overlooked that pharmaceutical progress does not only consist of the development of new active substances, but it also means that available active substances are utilised in the best possible way. Even though the specific reasons for the development of new pharmaceutical forms may be different, the ultimate goal is always to improve the utilisation of a specific substance. The individual considerations for the introduction of new pharmaceutical forms may roughly be grouped to four different categories:

- to enable new indications
- to enable the use in new patient groups
- to improve pharmacologic aspects (pharmacodynamics, pharmacokinetics)
- to facilitate the administration of a substance

It is understood that the motivation for the development of a new pharmaceutical form may not always be strictly assigned to a single of these categories. For example, there may be an overlap where a new pharmaceutical form is intended to facilitate the administration of a substance with the goal to allow its use in a new patient group. However, these four categories reflect the main aspects.

New indications

When new active substances are introduced into the market their pharmaceutical form is usually adapted to their specific indication. However, during the life cycle of a substance it may be discovered that it is also effective in other indications. In these cases, the available pharmaceutical form of the substance may not be suitable for this new indication. For example doxepin was initially introduced in the 1960s as an antidepressant [6]. Since that time, it is widely available in pharmaceutical forms that allow a peroral use. Later on it was reported that topically applied doxepin cream was effective against pruritus in atopic dermatitis [7]. Consequently, in 1994 the Food and Drug Administration (FDA) approved *Zonalon* a topical doxepin cream indicated for the treatment of pruritus in atopic dermatitis [8]. This is an example where a new pharmaceutical form was introduced for a known substance with the primary goal to achieve a new indication for the substance.

New patient groups

Not all pharmaceutical forms are equally suitable for all patient groups. There are even some patient conditions that do not allow the use of certain pharmaceutical forms. The most prominent example of patient groups in this context are paediatric patients. It is obvious that not all pharmaceutical forms are equally accepted across all age groups. Therefore, substances that specifically target a paediatric indication require the development of suitable pharmaceutical forms. The development of suitable paediatric pharmaceutical forms may even be imposed in paediatric investigation plans (PIP). But it should also be kept in mind that elderly patients suffer from age specific disabilities (e.g. dysphagia) that should be addressed by appropriate pharmaceutical forms [9].

Improvement of pharmacologic aspects

Pharmacology addresses the interaction between the human body and administered substances. Whereas pharmacokinetics describes the action of the body on the substance and pharmacodynamics describes the action of the substance on the body. The pharmaceutical form might have a significant impact on the pharmacokinetic profile of a substance and consequently also on its pharmacodynamic effects. The development of new pharmaceutical forms might therefore be used to improve pharmacologic aspects of a substance. For example, levodopa/carbidopa is usually available in peroral pharmaceutical forms for the treatment of Parkinson's disease. However, with the oral administration of levodopa/carbidopa constant blood levels will usually not be achieved. This may lead to fluctuations of the therapeutic effect which might clinically result in so called 'on-off' phenomena in certain patients. In order to improve the pharmacokinetics and to assure a constant supply, levodopa/carbidopa was developed as an intestinal gel [10]. The intestinal gel, administered with a pump via a permanent jejunal tube, allows a constant supply of the substances and may help to reduce dyskinesia [11]. This example demonstrates how the development of new pharmaceutical forms can successfully be used to improve pharmacologic aspects of a substance.

Facilitation of drug administration

Another goal for the development of new pharmaceutical forms is to facilitate the administration of substances. An example may be the development of a chewable tablet of acetylsalicylic acid which allows the intake without water. This may be considered an advantage in situations where no water is readily available (e.g. during travels) or where patients prefer a discrete drug administration. Furthermore, it does not require a tablet to be swallowed which may be a nuisance for some patients. Another example is the development of pharmaceutical forms that do not require any further preparation steps prior to administration. In cases where the manufactured dose form is a 'powder for solution for infusion' a reconstitution of the medicinal product is required. This is not only time consuming, but it also bears the risk of particulate or microbiological contamination during the preparation

process. In this context the development of a manufactured dose form as 'solution for infusion' would not only save time but it would also improve safety aspects.

1.2 Problem statement

When new active substances are authorised as medicinal products there is still limited knowledge about the safety and efficacy profile of these substances. This is due to the fact that the patient population included in the clinical development program just represents a minor fraction of the entire patient population that is exposed to the product once it is placed on the market. This emphasises the particular importance of pharmacovigilance especially in the early marketing phase of medicinal products containing new active substances.

In contrast to that, known active substances usually have a better characterised efficacy and safety profile, especially in cases with a well-documented continuous use over several decades. This valuable gain of knowledge comprises toxicological effects, efficacy in on and *off label* indications, tolerability of the drug substance in certain concomitant diseases, drug-interactions and many more. For older substances this information is usually available in the public domain.

Due to this widely available information it should be assumed that the development of new pharmaceutical forms of known active substances is associated with relatively low efforts for the industry. Furthermore, patients may benefit from an optimised utilisation of well-characterised substances. A lot of old active substances have been developed quite successfully in a new pharmaceutical form over the last period of years. However, there are still many old active substances for which no new pharmaceutical forms are developed despite a definitive clinical need.

For example in the field of emergency medicine intranasal drug administration is gaining more and more popularity, not only for paediatric patients [12]. However, there are almost no medicinal products authorised for intranasal administration in this discipline. This has led to a significant *off label* use of intravenous solutions for the intranasal route. The clinical relevance of intranasal drug administration is reflected by a vivid exchange of recommendations amongst

physicians on the *off label* use of intranasal drug administration, e.g. www.intranasal.net. There are even CE marked medical devices that allow intranasal administration of intravenous solutions with a regular syringe, like the *Nasal Intranasal Mucosal Atomization Device* (MAD) from Teleflex [13]. Although manufacturers emphasise that these devices may only be used with medicinal products authorised for the intranasal route it may be assumed that there is a considerable *off label* use. In Germany for example, MADs are part of the standard emergency equipment [14] whereas at the same time almost no medicinal products are authorised for an intranasal administration in the setting of emergency medicine.

1.3 Aim of the thesis

The aim of this thesis is to identify and describe potential regulatory challenges that might arise in the development of new pharmaceutical forms of known active substances within the EU. Potential legal bases for marketing authorisation applications (MAA) will be discussed and measures to protect medicinal products from competitors will be described. Furthermore, it will be evaluated in how far scientific guidelines support the development of new pharmaceutical forms. Last but not least strategies of marketing authorisation holders will be described who have successfully achieved marketing authorisation for a new pharmaceutical form of an old active substance.

2 Definition and Differentiation of Key Terms

In the context of new pharmaceutical forms a common understanding of associated key terms is important. Some of these terms are frequently mixed up or used inappropriately. Therefore, the definitions of these terms will be described in the following.

2.1 Pharmaceutical dose form

The *pharmaceutical dose form* is synonym with the term *dosage form* [15]. It describes the physical manifestation of a medicinal product. It has to be noted that for certain medicinal

products the term splits down to the *administrable dose form* (i.e. the form that is administered to the patient) and to the *manufactured dose form* (i.e. form that is manufactured). For example, if the *manufactured dose form* is a 'powder for oral solution' the *administrable dose form* is an 'oral solution', whereas for a 'buccal tablet' both forms would be identical. It has to be noted that the *pharmaceutical dose form* per se does not allow in all cases to conclude on the route of administration. E.g. the *pharmaceutical dose form* 'solution for injection' can apply for medicinal products that are administered intravenously but also for products that are administered epidural.

2.2 New dosage form

Considering the definition of *dosage form* above, it is interesting that the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q1C on 'Stability Testing for New Dosage Forms' defines a *new dosage form* as a product containing the same active substance with a

> *"different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate release tablet to modified release tablet) and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension)"* [16]

At the first glance this seems to be confusing as a simple change in the administration route would make a product a *new dosage form* although the actual *dosage form* might be the same. For example a product of lidocaine 'solution for injection' used for the intravenous route (e.g. as antiarrhythmic) would be considered a *new dosage form* compared to a product of lidocaine 'solution for injection' used for the epidural route (e.g. for epidural anaesthesia) although both *dosage forms* would actually be identical.

2.3 Pharmaceutical form

According to the standard terms of the European Directorate for the Quality of Medicines & HealthCare (EDQM) the *pharmaceutical form* describes the *pharmaceutical dose form* in a

more general aspect [15]. The *pharmaceutical form* can mean a *pharmaceutical dose form*, but it can also refer to products that actually consist of more than just one *pharmaceutical dose form* (combined pharmaceutical dose forms). For example, a medicinal product consisting of a 'tablet and solvent for rectal suspension' can be considered to be of a single *pharmaceutical form*. Also, standard terms of *pharmaceutical dose forms* that are extended by a packaging type (combined terms) are considered to be a *pharmaceutical form*. For example, a 'solution for injection in pre-filled pen' would be a different *pharmaceutical form* than a 'solution for injection in pre-filled syringe' although the *pharmaceutical dose form* would be identical.

2.4 Unit of presentation

The term *unit of presentation*, often referred to as only *presentation*, describes the countable entity of a medicinal product that is used as a basis to express the product's strength or quantity [15]. An example for a *unit of presentation* is 'actuation' for metered-dose inhalers. EDQM points out that some standard terms for the *unit of presentation* may be identical to the standard terms of other concepts. For example, 'patch' is a standard term for the *unit of presentation* as well as for the *pharmaceutical dose form* concept or 'bag' is a standard term for the *unit of presentation* as well as for *packaging* concept. However, it is emphasised that the *unit of presentation* shall be considered a separate concept that should not be mixed up with other concepts.

2.5 Route or method of administration

According to EDQM the *route of administration* describes *"the part of the body on which, through which or into which the medicinal product is to be introduced"*, whereas it is stated that the *method of administration* is mostly used for veterinary medicinal products *"to indicate the way the medicinal product is to be administered to the animals"* [15]. Both together form the standard term concept of *route or method of administration* without any further hierarchy of terms. In contrast to that, the 'Guideline on Summary of Product Characteristics (SmPC)' describes the *route of administration* as a subset of the *method of administration* [17]. Furthermore, the guideline implies a wider definition of the *method of administration*, as the

corresponding subsection in section 4.2 of the SmPC shall also contain information about special precautions related to the manipulation or administration of the product, information on methods to facilitate administration or acceptability, specific recommendations for use related to the pharmaceutical form and if parenteral products are concerned information on the infusion/injection rate as well as on the maximal concentration that can be used for children.

2.6 Formulation

The *formulation* is not part of the EDQM standard terms and it does not seem to exist a regulatory definition of this term. However, the term *formulation* is usually used to describe the specific composition of the active substance and its excipients. It is important to note that the *formulation* is clearly different from the concept of *pharmaceutical forms*. Even though a change of the *pharmaceutical form* often requires a change of the *formulation* there is no general dependence between both concepts. There are cases where the *formulation* changes without a change of the *pharmaceutical form*, e.g. when new excipients are used in a 'solution for injection' to allow a storage outside the refrigerator. At the same time there are cases where the pharmaceutical dose form changes without a change of the formulation, e.g. where the same *formulation* is used in one product as 'solution for injection' and in another product as 'oral solution'.

3 Legal Bases for Marketing Authorisation Applications

Articles 8, 10, 10a, 10b and 10c of Directive 2001/83/EC set out the different legal bases for MAAs. The choice of the legal basis is one of the most important regulatory decisions of the applicant. The legal basis does not only impact the regulatory procedure of the assessment of the application, but it also has significant influence on the development phase of the medicinal product as well as on its post-marketing phase. The legal basis implies the type and extend of non-clinical and clinical data required to support the MAA, the requirement for a PIP, the need

for a suitable reference medicinal product as well as market protection and data exclusivity periods.

In the following, the different legal bases will be discussed in the light of MAAs for new pharmaceutical forms of known active substances.

3.1 Stand-alone application according to Article 8(3)

Article 8(3) of Directive 2001/83/EC describes the so called 'stand-alone' application. For this application type there are no prerequisites regarding the existence of a suitable reference medicinal product or the extend of information available in the public domain. A stand-alone application requires a complete documentation of quality, safety and efficacy. This documentation is usually based on the applicant's own data. However, it is possible to substitute own data by bibliographical references [18]. This approach is called 'mixed application' but it follows the same legal requirements as set out in Article 8(3).

Due to the absence of external prerequisites a stand-alone application is generally applicable for any type of medicinal product. However, it may not in all cases be particularly suitable for new pharmaceutical forms of known active substances. This is because the generation of own data, i.e. the conduct of (non-)clinical studies, is relatively expensive and time consuming. Especially for the introduction of non-complex new pharmaceutical forms where no new indication is intended for the active substance it might be more suitable to refer to a reference medicinal product instead and to generate only the additional data that is required (see chapter 3.3 below). On the other hand, a MAA based on Article 8(3) for new pharmaceutical forms of known active substances can be considered in cases where complex or innovative pharmaceutical forms are to be introduced, especially when they are combined with new indications. These cases anyhow require a significant amount of new data to be generated by the applicant. Furthermore, potential reference products would be so different from the new product that a 'hybrid' application would not add any value. Where a stand-alone application is chosen for these cases, the option of a mixed application definitely makes sense. Especially for older substances there is usually a large amount of data available in the public domain.

Consequently, the applicant is not required to generate new data for each and every aspect of his product but instead he may substitute some of this data by bibliographical references.

Another drawback of stand-alone applications from the perspective of the applicant is the requirement for a PIP. The measures imposed in a PIP can be associated with significant financial efforts. This aspect is of particular interest in the context of new pharmaceutical forms of known substances. Patents for these products usually do not qualify for a supplementary protection certificate (SPC). This is because the marketing authorisation of these products cannot be considered to the first marketing authorisation of the corresponding substance[1]. Consequently, even if the PIP would be completed these products cannot benefit from an extension of the SPC as a reward for PIP completion.

Taken together, the choice of MAAs following the legal basis of Article 8(3) for new pharmaceutical forms of known active substances should be carefully considered on an individual basis.

3.2 Generic application according to Article 10(1)

Article 10(1) of Directive 2001/83/EC sets out that neither non-clinical nor clinical data are required for a MAA of generic products. However, paragraph 2(b) of that Article requires a generic product to be of the same pharmaceutical form as a reference medicinal product. Hence, an application of a product with a new pharmaceutical form of a known active substance cannot be filed based on Article 10(1).

3.3 Hybrid application according to Article 10(3)

In cases where the definition of a generic medicinal product is not met or in cases of further deviations from the reference medicinal product (e.g. new therapeutic indication), Article 10(3) of Directive 2001/83/EC sets out that appropriate new non-clinical and/or clinical data should be provided. As this type of application relies on a reference medicinal product as well

[1] Article 3(d) of Regulation (EC) No 469/2009, as amended

as on new data it is called 'hybrid' application and corresponding medicinal products are sometimes referred to as 'hybrid' products.

The new non-clinical and clinical data introduced by the applicant of the hybrid MAA focuses on two aspects. One aspect are bridging studies allowing the applicant to claim certain data from the reference medicinal product. The other aspect is that newly introduced data shall support the proposed differences between the hybrid and the reference medicinal product. Annex II of Volume 2A, Chapter 1 of the Notice to Applicants (NtA) specifies the type of additional data that is usually required for hybrid applications, depending on the proposed changes in contrast to the reference medicinal product. For different routes of administration and/or different pharmaceutical forms clinical safety and efficacy data, pharmacokinetic data and non-clinical data (e.g. data on local tolerance) shall be considered.

Taken together, hybrid applications following the legal basis of Article 10(3) are suitable for new pharmaceutical forms of known active substances. In contrast to stand alone-applications applicants are only required to introduce new data to allow a bridging to the reference product and to support the differences between the hybrid and the reference product. However, a hybrid application may not be suitable for products with a complex or innovative new pharmaceutical form especially if they come together with a new indication for the specific substance. In these cases, a potential reference medicinal product may be too different from the new product.

No PIPs are required for applications following Article 10(3)[2].

3.4 Well-established use application according to Article 10a

Article 10a of Directive 2001/83/EC sets out conditions under which MAAs can be solely based on bibliographic references. This type of application can be used for medicinal products containing an active substance that has been in 'well-established medicinal use' for ten years or longer and that has a recognised safety and efficacy profile. The central question of this type

[2] Article 9 of Regulation (EC) No 1901/2006, as amended

of application is what constitutes a well-stablished medicinal use. In Annex I of the aforementioned Directive it is specified that the time over which a substance has been used, the quantitative aspect of the use of the substance, the degree of scientific interest in the use of the substance and the coherence of scientific assessments shall be considered in order to demonstrate a well-established use. Additionally, in the NtA it is highlighted that the well-established use of a substance has as to be demonstrated in a specific therapeutic indication [18]. This means a substance per se cannot be considered to be in well-established use but only a substance in a specific therapeutic use. Consequently, an entirely new therapeutic indication cannot be introduced in MAAs following the legal basis of Article 10a. Furthermore, it is clarified in the NtA that a well-established medicinal use does not necessarily mean a use covered by a marketing authorisation.

In order to discuss a well-established use application in the light of new pharmaceutical forms it is helpful to differentiate between a 'new' pharmaceutical form and an 'entirely new' pharmaceutical form. Whereas

- a new pharmaceutical form is a pharmaceutical form that has not yet been authorised for a specific substance and
- an entirely new pharmaceutical form is a pharmaceutical form of a specific substance that has neither been authorised nor described in literature for that specific substance.

Considering the above, a MAA for a new pharmaceutical form of a known active substance can follow the legal basis of Article 10a of Directive 2001/83/EC, provided the combination of the pharmaceutical form, the specific substance and the specific therapeutic indication can be considered to be in well-established medicinal use. I.e. in these cases, it is possible to introduce a new pharmaceutical form of a substance via a well-established use application even if that specific pharmaceutical form has never been authorised for that substance before.

The introduction of entirely new pharmaceutical forms via a well-established use application is neither explicitly addressed in Directive 2001/83/EC nor in the NtA. However, the change of the pharmaceutical form of a substance for which a well-established use has been demonstrated can have a significant impact on its safety and efficacy profile. For example if

substance ‘A’ has been shown to be in well-established use for the treatment of ‘B’ in the pharmaceutical form of a tablet it seems to be obvious that it does not allow to claim safety and efficacy of substance ‘A’ for the treatment of ‘B’ in the form of a solution for injection. Consequently, *“recognised efficacy and an acceptable level of safety”* as required by Article 10a cannot be claimed for entirely new pharmaceutical forms.

However, the question remains whether this holds true for any change to the pharmaceutical form. Interestingly, it is stated in the NtA that

> *“In certain cases, studies may be provided only to support the relevance of the literature […], to the product intended for marketing.”* [18]

This implies that a certain degree of deviation between the product used in the literature and the product intended for marketing may be accepted, even though it is stated in the NtA that the possibility to provide own studies shall be decided on a case by case basis. It might be adequate in this context to refer to the definition of a generic medicinal product as set out in Article 10(2)(b) of Directive 2001/83/EC. There it is stated that various immediate-release oral pharmaceutical forms shall be considered to be of the same pharmaceutical form. If this notion of the ‘same pharmaceutical form’ would be applied to Article 10a it might eventually be possible to introduce an entirely new pharmaceutical form via a well-established use application, provided that the pharmaceutical form for which a well-established use has been demonstrated and the entirely new pharmaceutical form are both immediate-release oral pharmaceutical forms.

However, in the NtA it is highlighted that the legal basis of Article 10a is considered a derogation. Therefore, the corresponding provision shall be interpreted cautiously and the applicability of Article 10a for the MAA of a specific product is always to be decided on a case by case basis [18].

3.5 Application for fixed combination medicinal products according to Article 10b

Article 10b of Directive 2001/83/EC sets out a legal basis for the MAA of combination medicinal products. In order to utilise this legal basis for a MAA it is required that the single active

substances are already authorised medicinal products. Furthermore, the active substances included in that combination have to be in one and the same administrable dose form, so called 'fixed combination' [18]. In MAAs following the legal basis of Article 10b no data on the single substances have to be submitted. However, a full dossier shall be provided with regard to the combination.

Except for the requirement of the active substances to be in the same administrable dose form there are no further constraints regarding the pharmaceutical forms. Notably, the pharmaceutical form of the fixed combination is independent of the pharmaceutical forms of the authorised medicinal products of the single substances. Consequently, the legal basis of Article 10b can be used for MAAs introducing a new pharmaceutical for a combination of known active substances.

It has to be highlighted that combination medicinal products do not fall under the notion of the global marketing authorisation [18]. Therefore, periods of data exclusivity and market protection apply even if these periods have already elapsed for the single substances.

Applications following the legal basis of Article 10b require a PIP according to Article 7 of Regulation (EC) No 1901/2006.

3.6 Informed consent application according to Article 10c

Article 10c of Directive 2001/83/EC sets out the requirements for an 'informed consent application' where the MAH allows a third party to refer to his product regardless of any protection periods. However, it is explicitly stated in Article 10c that products submitted via an informed consent application need to be of the same pharmaceutical form as the product they refer to. Consequently, the introduction of a new pharmaceutical form of known active substances is not possible.

4 Protecting Strategies

As described above, the development of new active substances as well as the development of new pharmaceutical forms of known active substances is associated with enormous financial efforts for pharmaceutical companies. It follows a simple economic equation that the pharmaceutical entrepreneur tries to protect its products from competitors in order to avoid generic products to be placed on the market. On one hand it is necessary that developmental efforts and intellectual property can be protected as otherwise there would be no economic incentives for innovation. On the other hand, monopolistic situations have to be avoided which may negatively impact the affordability of medicines.

Interestingly, innovation and affordability of medicines are both part of the European Commission's Pharmaceutical Strategy for Europe [19]. This demonstrates the importance of balancing between these two obviously conflicting interests. In the following, the available protective measures will be described in the context of the development of new pharmaceutical forms of known active substances.

4.1 Data exclusivity

The period of data exclusivity is defined in Article 14(11) of Regulation (EC) No 726/2004 and in Article 10(1) of Directive 2001/83/EC. It describes an eight-year period following the marketing authorisation of a medicinal product in which this product may not be used as reference product. In other words, no MAA may be filed that relies on an authorised medicinal product whose data exclusivity period has not elapsed. Data exclusivity periods have to be interpreted under the notion of the 'global marketing authorisation' as set out in Article 6(1) of Directive 2001/83/EC. This is of special interest in the context of the development of new pharmaceutical forms of known active substances. Article 6(1) states that any new pharmaceutical form, administration route or presentation of a medicinal product that has been granted an initial marketing authorisation shall belong to the same marketing authorisation. Consequently, companies developing new pharmaceutical forms may not rely on data exclusivity in cases where the data exclusivity period has already elapsed for their

initial (i.e. global) marketing authorisation of the substance. However, the concept of global marketing authorisation is only applicable for medicinal products of the 'same' marketing authorisation holder [18]. This means that a new pharmaceutical form developed by a company does not fall under the global marketing authorisation of another company. But it is important in this context to note the definition of the 'same' marketing authorisation holder or applicant as set out in the NtA. Even companies that do not belong to the same company group can be considered the 'same' if for example agreements exist on a joint marketing or a licensing of a medicinal product [18].

Taken together, new pharmaceutical forms of known active substances may benefit from data exclusivity as long as they do not fall under a global marketing authorisation. In these cases, the new pharmaceutical form may not be used as a reference product within the first eight years following its authorisation.

However, a potential data exclusivity period for a product should not only be considered in the context of a global marketing authorisation but also in the context of the legal basis on which the MAA is based. Neither Directive 2001/83/EC nor Regulation (EC) No 726/2004 state that the 'granting' of a data exclusivity is subject to a certain legal basis. However, it follows from the NtA that data exclusivity only plays a role in the context of medicinal products authorised according to Articles 8(3), 10a, 10b or 10c of Directive 2001/83/EC. This is because only medicinal products authorised in accordance to these legal bases may be chosen as reference medicinal products [18].

On this background it is interesting to take a closer look at hybrid applications according to Article 10(3) of Directive 2001/83/EC. This is a suitable application type for new pharmaceutical forms of known active substances. As set out above, a hybrid application relies on a reference medicinal product but also new data can be filed, for example local tolerance studies or comparative bioavailability studies etc. to justify a new pharmaceutical form. Despite the fact that the generation of this new data can be associated with significant financial efforts for the applicant, no data exclusivity period is applicable in this case[3]. In the NtA it is explicitly stated

[3] unless Article 10(5) of Directive 2001/83/EC, as amended applies

that no periods of exclusivity apply for data that was generated to support a product authorised on the basis of Article 10(3) of Directive 2001/83/EC [18]. Furthermore, a pathway is described how products authorised via Article 10(3) can 'indirectly' serve as reference medicinal product [18]: Given the case the originator 'O' holds a MA for a medicinal product 'o' and company 'H' holds a MA for a hybrid product 'h' with 'o' as reference medicinal product, any other company 'X' can file a hybrid application for product 'x' with 'o' as reference medicinal product and with also referring to 'h'. The MAA of 'x' will formally be a hybrid application according to Article 10(3) of Directive 2001/83/EC however, actually 'x' can be considered a generic of 'h'. No period of data exclusivity applies for 'h'[3].

This means MAHs who generated data supporting a new pharmaceutical form of a known active substance do not benefit from periods of market exclusivity if the application was based on Article 10(3). There are only two exceptions. An exception applies to cases where significant non-clinical or clinical studies have been conducted to establish a new therapeutic indication. For these products a data exclusivity period of one year is granted if as set out in Article 10(5) of Directive 2001/83/EC. Another exception applies to cases where a paediatric use marketing authorisation was achieved (see chapter 4.3 below).

4.2 Market protection

Market protection is a 10-year period that follows the MA of a medicinal product set out in Article 10(1) of Directive 2001/83/EC or Article 14(11) of Regulation (EC) No 726/2004. During the period of market protection of an originator product corresponding MAAs of (hybrid) generic products may be submitted, processed and authorised, however these products may not actually be placed on the market [20]. In the context of new pharmaceutical forms of known active substances the general considerations for market protection follow the ones as set out above for data exclusivity.

4.3 Paediatric use marketing authorisation

The paediatric use marketing authorisation (PUMA) has been introduced with the paediatric Regulation (EC) No 1901/2006. Products that are not protected by a supplementary protection certificate or by patents that qualify for a supplementary protection certificate and that are developed exclusively for the paediatric population may apply for a PUMA[4]. This implies that PUMA primarily targets known active substances and tries to improve their paediatric utilisation. Consequently, a PUMA is relevant when discussing new pharmaceutical forms of known active substances - especially, when considering the fact that the paediatric use of a substance often requires dedicated pharmaceutical forms.

Article 30(3) Regulation (EC) No 1901/2006 sets out that the application for a PUMA can follow the legal basis of a hybrid application. This is of particular interest in the context of the rewards granted to products that achieved a PUMA. Article 38 points out that these products benefit from the full data exclusivity and market protection periods as described in Article 14(11) of Regulation (EC) No 726/2004 or Article 10(1) of Directive 2001/83/EC. This is remarkable because generally products authorised on the legal basis of a hybrid application do not benefit from this kind of protection (see chapter 4.1 above).

Taken together, the concept of PUMA seems to appear as an attractive regulatory pathway. However, it was reported that the response to PUMA is rather disappointing [21]. This was mainly attributed to the market's pricing pressure for established substances.

4.4 Patents and supplementary protection certificates

Patents

In Europe, patents can be granted for inventions in all technical fields[5]. However, it has to be demonstrated that the invention is novel, involves an inventive step and that it is industrially applicable[5]. Patents protect intellectual property by prohibiting third parties to make commercial use of foreign inventions. This is an important driver of innovation because it

[4] Article 2(4) of Regulation (EC) No 1901/2006, as amended
[5] Article 52(1) of the Convention on the Grant of European Patents (European Patent Convention), as revised

allows patent holders to exclusively utilise the investment they have put into their invention. European patents are usually valid for a 20-year period following the filing of the application[6]. However, the development of new active substances takes approximately 12 to 13 years [1], whereas the effective use of the patent just starts with the marketing authorisation of the final product. This virtually results in a reduction of the effective patent term for the product.

Supplementary protection certificates

In order to counterbalance this effect, the legislator has introduced a supplementary protection certificate (SPC) via Regulation (EC) No 469/2009. The SPC is not a temporal extension of a patent but it protects medicinal products after their corresponding patent has expired. It interdicts third parties to put a corresponding medicinal product on the market or to use a corresponding substance as a medicinal product[7]. The SPC is associated with a specific patent and it becomes effective as soon as the corresponding patent expires. The duration of the SPC equals the time period that has elapsed between the patent application and the first marketing authorisation of the corresponding medicinal product minus five years[8]. However, the SPC will not exceed a total duration of five years[9]. Considering the above, an SPC can prolong exclusivity of a medicinal product (i.e. patent + SPC) for up to 15 years following its MA (with an additional option of a six-months extension, see below).

SPC - Prerequisites

As set out in Article 3 of Regulation (EC) No 469/2009 an SPC will only be granted if certain requirements are fulfilled. First of all, only three patent types can qualify for an SPC, i.e. substance patents (patents of the substance itself), process patents (patents for the synthesis of the substance) or usage patents (patents for the use of the substance in a specific application). Furthermore, the product must not have been granted an SPC before.

[6] Article 63(1) of the Convention on the Grant of European Patents (European Patent Convention), as revised
[7] Article 4 of Regulation (EC) No 469/2009, as amended
[8] Article 13(1) of Regulation (EC) No 469/2009, as amended
[9] Article 13(2) of Regulation (EC) No 469/2009, as amended

Additionally, the substance must be authorised as a medicinal product, but it shall be the first authorisation of that substance as a medicinal product.

SPC - New pharmaceutical forms of known substances

As described above, new pharmaceutical forms of known active substances usually do not benefit from regulatory data exclusivity or market protection. This may be due to the fact that the new formulation either falls within the global marketing authorisation (whose data exclusivity and market protection periods have already expired) or the new formulation is filed as a hybrid application for which data exclusivity or market protection periods do not apply. Consequently, for new pharmaceutical forms of known active substances patents play a significant role for the protection strategy of the product. However, patents related to new pharmaceutical forms of known active substances do not qualify for an SPC. This is because these patents usually do not constitute 'basic patents' (i.e. substance patents, process patents or usage patents) and the MA of the new pharmaceutical form is per definition not the first MA of that specific substance. The fact that new pharmaceutical forms of known active substances do not qualify for an SPC may be justified by considering shorter development timelines for new pharmaceutical forms compared to the development timelines of entirely new substances. Consequently, the time span where a patent cannot effectively be used (i.e. between patent application and the first MA of the corresponding product) is shorter for new pharmaceutical forms of known active substances than for medicinal products containing new substances.

SPC - Case law

Interestingly, there have been cases where pharmaceutical companies have actually tried to claim SPCs for their medicinal products although the medicinal product was not a new active substance. For example, Abraxis Bioscience has developed a new formulation (that also constituted a new pharmaceutical form) of paclitaxel in 2008. Abraxis argued that the corresponding MA was the 'first' authorisation of that product according to Article 3(d) of Regulation (EC) No 469/2009. Abraxis concluded that the nanoparticle formulation of paclitaxel with albumin constitutes a 'new' product. However, the Court of Justice of the European Union judged that a MA of a new formulation of an old active substance does not

qualify as the first MA of that product in the notion of Article 3(d) of Regulation (EC) No 469/2009[10]. Consequently, no SPC was granted to Abraxis' new formulation of paclitaxel.

SPC - Paediatric regulation

Generally, if a PIP has been completed and a full compliance check has been conducted a six-months extension can be granted for the corresponding SPC according to Article 36(1) of Regulation (EC) No 1901/2006. However, paragraph 3 of that Article sets out that the granting of the extension is bound to the condition that the product is authorised in all Member States. This condition is supposed to improve availability of paediatric medicines throughout the EU.

Considering the fact that new pharmaceutical forms of known active substances usually do not benefit from SPCs they can also not benefit from rewards for PIP completion. However, it is acknowledged that a majority of MAAs for new pharmaceutical forms of known active substances are probably authorised on the basis of a hybrid application and consequently do not require a PIP. But there are some more complex new pharmaceutical forms of known active substances whose MAA was filed on the basis of Article 8(3) of Directive 2001/83/EC, e.g. see *Ionsys* below. These types of products require a PIP according to Article 7 of Regulation (EC) No 1901/2006 but at the same time these products cannot benefit from a six-months extension of an SPC as they do not qualify for an SPC.

[10] Court of Justice of the European Union ECLI:EU:C:2019:238

Legal bases of Directive 2001/83/EC	Applicable for new pharmaceutical forms of known active substances?	Data exclusivity / market protection	Further aspects
Stand-alone application Article 8(3)	yes	8/10 years new pharmaceutical form falls within global MA	PIP required, mixed application possible, more suitable for innovative/ complex new pharmaceutical forms
Generic application Article 10(1)	**no**	-/-	-/-
Hybrid application Article 10(3)	yes	Art. 10(3) products cannot be used as RMP, but data generated to support an Art. 10(3) MAA can be referred to by competitors - no data exclusivity applies in this case	no PIP required, more suitable for non-innovative / non-complex new pharmaceutical forms, suitable RMP required
Well-established use application Article 10a	yes (if the pharmaceutical form is part of the well-established use)	8/10 years Art. 10a products can serve as RMP but competitors may base their application for the same product also on Art. 10a	no PIP required, requires documentation of a well-established use for the combination of substance, indication and pharmaceutical form
Fixed combination Article 10b	yes	8/10 years independent of the global marketing authorisation of the single substances	PIP required, only applicable for combinations
Informed consent Article 10c	**no**	-/-	-/-

MA: marketing authorisation, MAA: marketing authorisation application PIP: paediatric investigation plan, RMP: reference medicinal product

Table 1: Potential legal bases for MAAs of new pharmaceutical forms of known active substances and their implications

5 Scientific Guidelines

The EMA issues scientific guidelines for the development of medicinal products in cooperation with the national competent authorities of the Member States. These guidelines are not legally binding (so called 'soft law') but they reflect current scientific knowledge and it is therefore strongly advised to justify any deviations. The EMA also implements guidelines harmonised by the ICH.

In the following, the scientific guidelines will be summarised that are related to the development of new pharmaceutical forms of known active substances.

5.1 Quality

Stability testing

The 'Note for Guidance on Stability Testing: Requirements for New Dosage Forms' is the European implementation of ICH guideline Q1C 'Stability Testing for New Dosage Forms' [16, 22]. The guideline states that products representing new dosage forms of known active substances should follow the stability testing as set out for new active substances and associated products, i.e. as defined in ICH guideline Q1A. The term 'new dosage form' as used in the guideline does not only refer to a change in the actual dosage form but also to changes in the route of administration or in the functionality of the delivery system (see chapter 2.2). The guideline leaves an option for a reduced stability testing of new dosage forms in *"justified cases"* without further specifying these. However, it is assumed that a reduced stability testing might be a reasonable approach in cases where the formulation of the product itself is unchanged. For example, if the original product is a solution for injection for the intravenous route and the new dosage form would be an oral solution but where the formulation itself would be identical between both products.

The guideline only applies to new dosage forms by owners of the original authorisation of the new active substance. This means the provision does not apply to generic companies that introduce a new dosage form according to Article 10(3) of Directive 2001/83/EC. In these cases

the provisions as laid down in the 'Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products' do apply [23].

Quality aspects of specific types of products

There is a group of guidelines that specifically address quality aspects of certain types of medicinal products [24]. Some of these may also be of relevance for the development of new pharmaceutical forms of known active substances, like the 'Guidelines on the pharmaceutical quality of inhalation and nasal products' [25], the 'Guidelines on quality of oral modified release products' [26] or the 'Guideline on quality of transdermal patches' [27].

5.2 Pharmaceutical forms for specific patient groups

Paediatrics

In order to support the development of medicinal products for children, the EMA has published corresponding guidance documents like the 'Guideline on pharmaceutical development of medicines for paediatric use' [28] or the 'Reflection paper: formulations of choice for the paediatric population' [29]. These documents are not only applicable when developing products with new active substances, but they also provide guidance in the development of new pharmaceutical forms of known active substances for a specific paediatric use.

The 'Guideline on pharmaceutical development of medicines for paediatric use' discusses a wide range of aspects of paediatric medicinal products, like the active substance, excipients or the route of administration and pharmaceutical forms. Whereas in the reflection paper specific formulations and pharmaceutical forms are discussed in more detail.

The reflection paper highlights the choice of the 'right' pharmaceutical form/route of administration which depends on a variety of different aspects. Complexity is increased by the fact that these aspects are not equally important in all paediatric age groups. Consequently, there is no single pharmaceutical form that fits to 'the' paediatric population. For example, in newborns, infants and toddlers the pharmaceutical form is primarily bound to the condition, that no (or a reduced) patient cooperation has to be expected for the administration of the product. Additionally, pharmaceutical forms/routes of administration that might be associated

with a risk of aspiration should be avoided in this age group. The reflection paper also points to the specific circumstances of schoolchildren. In this age group dosage forms should enable long dosing intervals so that a use of the medicinal product can be avoided during school day. However, if administration in school cannot be avoided, a simple administration procedure is of even more importance. This is because parents may be well trained in the administration of specific medicinal products whereas schoolteachers may not always be familiar with complex medicinal products of their pupils. During adolescence other factors come into play, like the wish of being independent from adults. This means medicinal products should be designed in a way that allows self-administration by adolescents. Furthermore, the reflection paper highlights the fact that adolescents may prefer dosing forms that enable a discrete administration of the product. However, the aspects mentioned above only represent a minor fraction of all the aspects that have to be considered in the paediatric population when it comes to the choice of the 'right' pharmaceutical form. The reflection paper concentrates all these different aspects in a table, presenting the pharmaceutical form/route of administration of choice for the different paediatric age groups. The table represents the core of the reflection paper as it provides a structured overview of suitable pharmaceutical forms at a glance. It can roughly be summarised that for very young children the focus is on parenteral pharmaceutical forms. With increasing age, the focus shifts over to suppositories and liquid peroral preparations. Thereafter, rectal preparations get less important and solid peroral preparations become more and more accepted.

However, it is emphasised that the reflection paper shall not be seen as a document defining regulatory requirements, but it rather serves as a basis for individual discussions of 'suitable' pharmaceutical forms for paediatric medicinal products.

Although not belonging to the scientific guidelines, another interesting collection of documents provided by the EMA is the 'Needs for paediatric medicines' [30]. The collection describes the specific paediatric needs in 16 medical fields. It also addresses the need of certain new pharmaceutical forms for specific substances.

Elderly patients

Considering the demographic change of western societies with increasing life expectancies, the focus of pharmaceutical development has also moved towards older patients. Just recently a guidance document has been issued for the development of medicinal products specifically for elderly patients: the 'Reflection paper on the pharmaceutical development of medicines for use in the older population' [31]. The paper describes specific conditions of older patients that should be considered when developing medicinal products for this patient group. Besides aspects like dosing frequencies, excipients, or container closure systems also the choice of the route of administration and the pharmaceutical form is described.

It is stated that the choice of a suitable pharmaceutical form requires to take into account common underlying conditions in the older population. This includes potential impairments of eyesight, mental cognition as well as motoric and/or sensory skills. Thus, products that require a correct dose to be measured before administration bear an increased risk of potential dosing errors and should be avoided. Likewise, products that require complex preparation steps before administration should be avoided if possible (e.g. withdrawal of a solution for subcutaneous injection from a vial). The reflection paper also highlights the importance of locally applied pharmaceutical forms. These allow a reduction of systemic exposure of a substance. This does not only play a role for reducing side effects but also for reducing the risk of potential drug interactions. Drug interactions are of special concern in elderly patients as it has been reported that almost 12% of the population above 65 years takes at least ten different medicinal products [32].

Taken together, the development of medicinal products intended for the elderly population requires to consider age specific conditions. The reflection paper can serve as a basis for the identification of suitable pharmaceutical forms of known active substances.

5.3 Local tolerance

The development of new pharmaceutical forms of known active substances can be associated with a new route of administration. In these cases, it may be required to provide the results of local tolerance tests. The 'Guideline on non-clinical local tolerance testing of medicinal

products' provides guidance for these kind of tests [33]. It is stated that local tolerance tests should usually not be conducted separately but preferably together with general toxicity studies. However, for MAAs of new pharmaceutical forms following Article 10(3) of Directive 2001/83/EC it might not be required to conduct general toxicity studies. Consequently, for these applications separate local tolerance studies may be required. The guideline also clarifies that investigations on local tolerance are usually not required for different pharmaceutical forms intended for the oral route of administration. Specific aspects of local tolerance tests are described for pharmaceutical forms intended for ocular use, for administration to the skin, transdermal systems as well as for intravenous, intramuscular or subcutaneous routes. For all other products the general considerations as set out in the guideline shall be applied.

5.4 Modified release dosage forms

The EMA has published a specific clinical guideline for modified release dosage forms 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms' [34]. The guideline aims at modified release dosage forms intended for oral, intramuscular, subcutaneous and transdermal use. It sets out the requirements for clinical data of these products. Three different scenarios are described in the guideline: 'applications for new modified release dosage forms of new chemical entities', 'applications for a modified release formulation of a drug that is authorised in a formulation with a different release rate' and 'abridged application for modified release forms referring to a marketed modified release form'. Consequently, this guideline is relevant for new pharmaceutical forms of known active substances where a modified drug release is intended. In cases where a modified release dosage form is intended for a substance that has been authorised with a different release rate pharmacokinetic studies shall address the rate and extent of absorption. Furthermore, inter-individual pharmacokinetic variability and factors that may influence the pharmacokinetic profile have to be identified. Also, efficacy studies are required in these cases. However, the guideline defines certain conditions that exceptionally allow to omit clinical efficacy studies. In these cases, efficacy can be claimed indirectly, provided sufficient knowledge of the exposure-effect relationship is available.

6 Examples of New Pharmaceutical Forms of Known Substances

6.1 Ionsys

Fentanyl

Fentanyl, is a potent opioid analgesic that was first described more than 50 years ago [35]. Since that time, it is primarily used as solution for injection via the intravenous route, either for analgesia during general anaesthesia or for analgesic treatment of ventilated patients on the intensive care unit. In the 1990's transdermal patches of fentanyl were developed [35]. This pharmaceutical form allowed the treatment of chronic pain syndromes due to the fact that the patients did not require an intravenous access. Furthermore, the transdermal patch allows a continuous administration of fentanyl to the patient. Unfortunately, with transdermal patches patients are not able to actively control the fentanyl administration, e.g. in situations with an increased pain intensity. Once the transdermal patch is attached to the skin a predefined rate of fentanyl continuously diffuses through the skin.

In contrast to this, iontophoretic transdermal systems can actively promote the migration of a substance through the skin by applying a low level electric field [36]. This technique allows patients to trigger the administration of predefined doses of the active substance whenever desired.

Initial marketing authorisation application

Ionsys is a transdermal system using iontophoresis for the administration of fentanyl. In July 2004 Janssen-Cilag International NV submitted the initial MAA of *Ionsys* to the EMA [37]. The application was based on Regulation (EEC) No 2309/93 and marketing authorisation was finally issued in January 2006 for the management of acute moderate to severe post-operative pain [38]. The non-clinical part of the initial application consisted of own data as well as on bibliographical references from the 1960's and 1970's [39]. Own data was generated for pharmacokinetics, primary pharmacodynamics and local tolerance studies. The clinical part of the application included 20 clinical studies, thereof four phase III studies. In the clinical development program, a total of 412 healthy volunteers and 1,153 patients were exposed to

Ionsys. At the time of MAA submission in 2004 no PIP was required as Regulation (EC) No 1901/2006 was not yet in place.

In 2009 marketing authorisation of *Ionsys* was suspended due to quality issues and the marketing authorisation expired in 2011 since the applicant did not apply for a renewal [40].

Second marketing authorisation application

In 2014 a new application for *Ionsys* was submitted to the EMA. The application was based on Article 8(3) of Directive 2001/83/EC as a complete and independent application [41]. Marketing authorisation was granted in November 2015 for management of acute moderate to severe post-operative pain in adult patients [42]. A PIP was agreed in May 2014 including a waiver for the age group from birth to less than 2 years [43]. The PIP included two quality measures and seven clinical trials. Completion of the PIP was deferred to September 2019.

Despite the fact that there were some technical modifications of the new *Ionsys* product, the new MAA was mainly based on the same data as the initial MAA [41]. Regarding the non-clinical part only the results of one carcinogenicity and two toxicology studies were included in the new application. These studies were still on-going at the time of the initial submission. The omission of any further new non-clinical data was accepted by the CHMP due to the reason that the formulation of fentanyl did not change.

Besides the old clinical data that was already presented in the initial submission there was also new clinical data submitted with the new MAA. Several post-marketing studies that were conducted with the initial *Ionsys* product after its approval back in 2006 were included in the new MAA. Furthermore, a bioequivalence study was conducted comparing the bioavailability of the initially authorised and the new modified *Ionsys* product. This was necessary because the quality issues related with the initial product required technical modifications of the application system. Additionally, there were several clinical studies conducted to examine adhesion and usability.

In 2018, three years after obtaining the marketing authorisation the applicant announced to permanently discontinue the marketing of *Ionsys* and the marketing authorisation was withdrawn subsequently [44].

Protecting strategy

The initial marketing authorisation for *Ionsys* was issued to Janssen-Cilag International NV (a Johnson & Johnson subsidiary) in 2006. At this point in time, protection periods for the transdermal fentanyl patch *Durogesic 25 mikrog/tunti depotlaastari* authorised on 24 May 1995 in Finland, MA-number 11792, have already elapsed [45]. Considering the fact that the marketing authorisation holder of *Durogesic* is Janssen-Cilag Oy it may be assumed that both marketing authorisations fall under the same global marketing authorisation. Consequently, no periods of data exclusivity or market protection applied to *Ionsys* when it entered the market.

The second MAA of *Ionsys* was submitted by Incline Therapeutics Inc. who acquired the worldwide rights for *Ionsys* by Johnson & Johnson [41]. Due to the corresponding agreements between both companies they are considered the same applicant / marketing authorisation holder in the context of the global marketing authorisation [18]. Consequently, also for the second MAA of *Ionsys* no periods of protection applied.

In 1996 ALZA Corporation filed a European patent application for an iontophoretic delivery system of fentanyl [46]. ALZA was the original developer of *Ionsys* and was acquired by Johnson & Johnson in 2001 [47]. The European patent that covered the *Ionsys* product, was finally granted in April 2004. Considering the date of filing the patent expired in 2016. The patent did not qualify for an SPC since *Ionsys* was not the first product of fentanyl placed on the market, i.e. the requirement of Article 3(d) of Regulation (EC) No 469/2009 was not met. Consequently, even if the PIP that was imposed within the second marketing authorisation procedure would have been completed, no reward could be received, i.e. a 6-month extension of the SPC.

Taken together, no periods of data exclusivity or market protection applied for *Ionsys*. Therefore, the main protection was the European patent that expired in 2016. Considering the initial marketing authorisation that was granted in 2006 the patent could have been effectively

used for approximately 10 years. At the time point of the second marketing authorisation of *Ionsys* in 2015 no regulatory protection applied and the corresponding patent was valid for only one more year.

6.2 Instanyl

Marketing authorisation application

Instanyl is a nasal fentanyl spray indicated for the management of breakthrough pain in oncologic patients. The MAA was filed to the EMA in November 2007 on the basis of Article 8(3) of Directive 2001/83/EC [48] and the product was finally authorised in July 2009 [49]. Eligibility to the centralised procedure was based on a demonstration of interest of patients at Community level. No PIP was required as Article 7 of Regulation (EC) No 1901/2006 only applied from 26 July 2008[11].

At the time point of filing of the application the indication of management of breakthrough pain in oncologic patients was not considered a new indication for fentanyl, as *Actiq* (a fentanyl lozenge) was authorised for the same indication in 2001 via a decentralised procedure[12].

Two local tolerance studies were conducted by the applicant. All other non-clinical aspects were covered by bibliographic references [48].

A total of 13 clinical trials were included into the MAA. Six of these trials were safety/efficacy studies in which 207 patients were exposed to *Instanyl*. Additionally, seven pharmacokinetic studies were conducted [48].

Protecting strategy

The marketing authorisation of *Instanyl* was granted to Nycomed Danmark ApS in July 2009. At this time point Nycomed already hold a marketing authorisation of a transdermal patch of fentanyl [50]. The transdermal patch was authorised as *Matrifen* in Sweden in September 2005, authorisation numbers 22732 and 21287 to 21290 [51]. Currently, Takeda is the MAH of

[11] Article 57(1) of Regulation (EC) No 1901/2006, as amended
[12] Procedure number DE/H/6124/001

Matrifen since Takeda acquired Nycomed in 2011 [52]. It is assumed that *Instanyl* and *Matrifen* both fall under the same global marketing authorisation. As *Matrifen* was authorised in Sweden before 30 October 2005[13], a 10-year period of protection applied [18]. This type of protection functioned as data exclusivity and was not supplemented by a separate period of market protection. Consequently, regulatory protection for *Instanyl* and *Matrifen* expired in 2015.

In 2008 a European patent was granted to Nycomed. The patent claimed fentanyl salts for nasal administration [53]. However, the patent claim had to be narrowed to fentanyl citrate following an opposition decision in 2011 [54]. Considering the fact that *Instanyl* actually contains fentanyl citrate the new patent specification still covered the product. Following a patent term of 20 years from date of filing the patent will expire end of July 2021.

Taken together, at the time point of marketing authorisation of *Instanyl* a regulatory protection of six years remained. Furthermore, a patent protection for 12 years applied effectively.

6.3 Zalviso

Sufentanil

Sufentanil is a very potent opioid analgesic that was first described in 1976 [55]. Since that time it is mainly used for the intravenous route but the epidural and subarachnoidal use has also been authorised for some sufentanil products [56]. The intravenous, epidural or subarachnoidal routes require a corresponding patient access. This makes the use of sufentanil inconvenient for patient controlled postoperative analgesia. On the other hand, conventional peroral pharmaceutical forms usually have a delayed onset of effect as the active substance needs to be absorbed from the gastrointestinal tract. In order to overcome this, Grünenthal introduced the sublingual sufentanil tablet *Zalviso*.

[13] Date of transposition according to Articles 2 and 3 of Directive 2004/27/EC

Marketing Authorisation

Zalviso is a sufentanil sublingual tablet indicated for the management of acute moderate to severe post-operative pain in adult patients. Due to the small size of the sublingual tablet and in order to position the tablet correctly under the tongue a dedicated administration device is required [57]. The administration device is an active medical device and CE marked as a class IIb product [58]. In June 2014 Grünenthal filed the MAA of *Zalviso* to the EMA [59]. The product was finally approved in September 2015 [60]. The eligibility to the centralised procedure was based on the demonstration of a significant technical innovation. The application followed the legal basis of Article 10(3) of Directive 2001/83/EC. The reference product which is or has been authorised for 6/10 years in the EEA is *Sufenta Forte solution for injection 0.05 mg/ml.* This product has been granted a marketing authorisation in the Netherlands in 1982. The reference product authorised in the Community/Member State where the application was made or European reference medicinal product is *Sufenta solution for injection 0.005 mg/ml*. This product has been granted a marketing authorisation in the Netherlands in 1978. No reference product for demonstration of bioequivalence was chosen as no bioequivalence studies were conducted. This was due to differences in the strength, daily dose, route of administration and indication between the reference products and *Zalviso* [59].

The non-clinical part of the MAA of *Zalviso* was mainly based on cross-references to *Sufenta*. Only few new pharmacokinetic studies were conducted in dogs in order to compare pharmacokinetics of the intravenous, oral, sublingual and buccal route. Additionally, some hamster studies were conducted for repeat-dose toxicity and local tolerance.

The clinical development program included seven phase I studies. In these studies, bioavailability, pharmacokinetics, pharmacodynamics and drug interactions were evaluated in a total of 159 healthy subjects. Additionally, three phase II studies and three phase III studies were conducted. In these a total of 764 patients were exposed to *Zalviso* [59].

Due to the choice of a hybrid application no PIP was required.

Protection Strategy

No periods of data exclusivity or market protection applied for *Zalviso* as it was authorised via Article 10(3) of Directive 2001/83/EC (see chapter 4.1). The Commission Decision did not include a statement on a new indication according to Article 10(5) of Directive 2001/83/EC [60].

Zalviso was initially developed by AcelRx Pharmaceuticals, Inc. who concluded a license agreement with Grünenthal for the EU in 2013 [61]. Grünenthal has just recently announced to terminate this agreement [62]. AcelRx holds a European patent for a small volume oral transmucosal dosage form of sufentanil for treatment of pain [63]. The patent describes potential dispensing devices very similar to the actual dispensing device of *Zalviso*. The patent was filed end of 2007 and it was actually granted to AcelRx in mid of 2010. Interestingly, Grünenthal already filed an European patent application in 2004 for a dosage form that is safeguarded from abuse [64]. The patent describes a tamper-proof container that can protect medicinal products with an abuse potential. Actually, *Zalviso* sublingual tablets come in a tamper-proof cartridge that might be covered by this patent [59].

Taken together, no periods of data exclusivity or market protection applied. Therefore, the protection strategy for *Zalviso* is solely based on patents. At the time point of marketing approval in 2015 two patents were in place. One of these patents will expire in 2027 and another in 2024.

6.4 Buccolam

Midazolam

Midazolam was introduced in the late 1970's as an intravenous agent for induction of anaesthesia [65]. The development of a peroral pharmaceutical form in the following years also allowed the therapy of sleep disorders [66]. Midazolam's anticonvulsive properties were also discovered relatively quickly after its introduction [67]. However, the challenge in the pharmacologic therapy of acute convulsive seizures is to find a suitable route of administration. Due to the seriousness of convulsive seizures (e.g. aspiration, hypoxia) a rapid onset of the anticonvulsive effect is required. This renders conventional peroral

pharmaceutical forms unsuitable. Furthermore, patients suffering from acute convulsive seizures are unable to swallow any medication. On the other hand, it is very difficult and time consuming to establish an intravenous access in patients suffering from acute convulsions. Additionally, intravenous drug administration cannot be performed by laypersons.

Buccolam addresses this challenge, it is an oromucosal solution of midazolam indicated for treatment of prolonged, acute, convulsive seizures exclusively in the paediatric population [68].

Marketing Authorisation Application

The MAA of *Buccolam* was submitted to the EMA in August 2010 [69]. The eligibility to the centralised procedure was based on an application for a PUMA as laid down in Article 31 of Regulation (EC) No 1901/2006. Interestingly, it was reported that *Buccolam* was the first product that was granted a PUMA via the centralised procedure [70]. The legal basis for the MAA was a hybrid application according to Article 10(3) of Directive 2001/83/EC. *Hypnovel 10mg/2ml solution for injection* was chosen as reference product not authorised for less than 6/10 years in the EAA and as reference product authorised in the Community/Member States where the application is made or European reference medicinal product. No reference medicinal product was chosen for bioequivalence studies. *Hypnovel* was authorised in 1982 in the United Kingdom. The proposed changes of *Buccolam* compared to the reference product were the therapeutic indication, the pharmaceutical form and the route of administration. Interestingly, the formulation of *Buccolam* is essentially similar to the reference medicinal product [69].

There was no new non-clinical data presented in the application dossier. All non-clinical aspects were sufficiently covered by bibliographic references. Clinical efficacy and safety of the oromucosal midazolam administration was demonstrated by referring to published data. This data was based on *Hypnovel 10 mg/2mL*. The applicant argued that no relative bioavailability or bioequivalence bridging studies of *Buccolam* versus *Hypnovel 10 mg/2mL* were required since both formulations are identical. However, a pharmacokinetic study with *Buccolam* had to be conducted for a better characterisation of the pharmacokinetic profile. In addition to the

aforementioned pharmacokinetic study the applicant conducted a computer-based simulation to predict exposure and pharmacokinetic linearity for different paediatric age ranges [69].

A PIP was agreed for *Buccolam* in August 2009 [71]. Usually a PIP is not required for MAAs following the legal basis of a hybrid application. However, there is an obligation for a PIP when applying for a PUMA[14]. A waiver was granted for children below three years of age. The PIP imposed the development of an age-specific pre-filled syringe and the conduct of a pharmacokinetic study for oromucosal midazolam administration in children from three months to 18 years undergoing elective surgery.

The PUMA for *Buccolam* was finally granted in September 2011 [72].

Protection strategy

Buccolam benefits from data exclusivity of 8 years plus 2 years of market protection as defined in Article 14(11) of Regulation (EC) No 746/2004. This results from an award for the PUMA according to Article 38(1) of Regulation (EC) No 1901/2006. The reward for a PUMA is granted irrespective of the legal basis of the application and irrespective of the global marketing authorisation. No European patents have been identified covering *Buccolam*.

[14] Article 30(2) of Regulation (EC) No 1901/2006, as amended

Product	Legal basis	Study program	Paediatric investigation plan	Protection at time point of MA	Remarks
Ionsys (initial application)	Regulation (EEC) No 2309/93	non-clinical: bibliographic data, several own studies for PK, primary PD and local tolerance clinical: 20 clinical trials of various phases	no (paediatric regulation not effective at time point of filing)	DE/MP: none (due to GMA) patents: valid for 8 more years	MA suspended due to quality issues, MAH did not apply for renewal, MA expired
Ionsys (second application)	Article 8(3) of Directive 2001/83/EC	mainly based on data from initial MAA, additionally: several clinical post marketing studies conducted with original product, 1 BE study (original vs. new product), several studies to evaluate usability and adhesion	yes, 2 quality and 7 clinical measures imposed	DE/MP: none (due to GMA) patents: valid for 1 more year	MA withdrawn on request of MAH for commercial reasons
Instanyl	Article 8(3) of Directive 2001/83/EC	non-clinical: bibliographic data, 2 local tolerance studies clinical: 13 clinical trials of various phases	no (paediatric regulation not effective at time point of filing)	DE/MP: 6/0 years (due to GMA) patents: valid for 12 more years	---
Zalviso	Article 10(3) of Directive 2001/83/EC	non-clinical: mainly based on RMP, own studies for local tolerance and comparative PK Clinical: 13 clinical trials of various phases	no (not required for Art. 10 applications)	DE/MP: none patents: valid for 12 more years	MAH (Grünenthal) has terminated the license agreement with the license holder (AcelRx)
Buccolam	Article 10(3) of Directive 2001/83/EC	Non-clinical: bibliographic data only Clinical: bibliographic data, 1 PK study	yes (due to PUMA) 1 quality and 1 clinical measure imposed	DE/MP: 8/10 years (due to PUMA) patents: none	first PUMA via centralised procedure

BE: bioequivalence, DE: data exclusivity, GMA: global marketing authorisation, MA(H): marketing authorisation (holder), MP: market protection, PD: pharmacodynamics, PK: pharmacokinetics, PUMA: paediatric use marketing authorisation, RMP: reference medicinal product

Table 2: Overview of examples of new pharmaceutical forms of known substances

7 Discussion

In certain points the European regulatory landscape is well adapted to the particularities of new pharmaceutical forms of known substances. For example, the legal basis of hybrid applications according to Article 10(3) of Directive 2001/83/EC offers a good opportunity to build on safety and/or efficacy of existing products and it only requires new data to be submitted for aspects where the hybrid product deviates from the reference product. Another regulatory provision that is particularly suitable for new pharmaceutical forms of known substances is the possibility of mixed applications. These allows applicants to replace certain data in the application dossier by bibliographical references when a stand-alone application according to Article 8(3) of Directive 2001/83/EC is chosen. This legal basis is of special interest in cases where the new pharmaceutical form of a known substance deviates in several major aspects from potential reference products, e.g. *Ionsys* or *Instanyl*.

Both, hybrid and mixed applications, help applicants to avoid the generation of redundant data, i.e. data that is already available for a reference product or that is already available in the public domain. This reduces financial efforts associated with the development of new pharmaceutical forms of known substances and consequently supports innovation and may reduce drug prices.

Another supportive regulatory measure is the provision of a wide range of scientific guidelines referring to new pharmaceutical forms. These guidelines cover quality, non-clinical and clinical aspects and help applicants to align their drug development already in the initial planning phase. Furthermore, the guidelines may prevent diverging expectations between regulatory authorities and applicants during the review process. This in turn may help to facilitate the approval process and to avoid extensive discussions between the applicant and regulatory authorities. Taken together, the available scientific guidelines enable an efficient drug development.

However, from the perspective of the industry, there are also challenges in the European regulatory landscape when it comes to the development of new pharmaceutical forms of known active substances. One of the most important is the limited eligibility for regulatory

protection of these products, i.e. data exclusivity and market protection. New pharmaceutical forms are often authorised according to Article 10(3) of Directive 2001/83/EC for which no periods of data exclusivity or market protection applies. However, even if a stand-alone application is chosen according to Article 8(3) of Directive 2001/83/EC, new pharmaceutical forms of known active substances often fall within the global marketing authorisation of the applicant, e.g. *Ionsys*. This means regulatory protection periods might have already elapsed or might elapse in near future.

The non-applicability of regulatory protection for hybrid products seems to be rational in cases where the MAA mainly relies on the reference product and only minor data is submitted to support the hybrid application. It is understood that hybrid or generic medicinal products that mainly or exclusively rely on a reference medicinal product should not benefit from regulatory protection. However, there are hybrid products that come with significant changes compared to the reference medicinal product and consequently require a significant amount of new data. For example, the MAA of *Zalviso* mainly relied on the non-clinical part of the reference medicinal product whereas a full package was delivered for the clinical part, i.e. seven phase I, three phase II and three phase III studies. Therefore, the question arises whether it is justified to categorically withhold regulatory protections for hybrid applications.

One may argue that in cases where a hybrid application just relies on minor aspects of the reference medicinal products the applicant could have also chosen a mixed application according to Article 8(3) of Directive 2001/83/EC. However, even in these cases regulatory protection might not apply due to the global marketing authorisation, e.g. see *Ionsys*. Furthermore, applications according to Article 8(3) require a PIP whereas new pharmaceutical forms of known active substances usually do not benefit from rewards granted for PIP completion, since corresponding patents do not qualify for SPCs. This makes a stand-alone application unattractive for new pharmaceutical forms of known active substances.

The limited opportunities for regulatory protection of new pharmaceutical forms of known active substances are counterbalanced by two legislative measures: the granting of one year data exclusivity for new indications according to Article 10(5) of Directive 2001/83/EC and the ‘full’ data exclusivity and market protection periods granted to products with a PUMA

according to Article 38 of Regulation (EC) No 1901/2006. However, both measures fall too short.

The one-year data exclusivity granted under Article 10(5) would only apply to new pharmaceutical forms of known active substances that come with a new indication (and if significant studies have been conducted). This implies that only the introduction of new indications is considered a meaningful innovation, but it completely ignores other potential patient relevant improvements that can be introduced by new pharmaceutical forms, like ease of handling, prolonged dosing intervals, enabling the use in emergency situations etc.. Although it is acknowledged that a 'new indication' according to Article 10(5) does not only refer to a new target disease but includes a slightly wider context [73]. Furthermore, the one-year data exclusivity may be too short to justify significant financial efforts for non-clinical or clinical studies especially in cases where no patent protection applies.

The second option to achieve regulatory protections for new pharmaceutical forms of known active substances is a PUMA. However, there is only a poor utilisation of the PUMA, indicating that the associated benefits are insufficient in the context of the high pricing pressure of non-patented substances.

On the background of these and other shortcomings of the paediatric regulation the European Commission is currently discussing a modification of the rewards and incentives system for the development of paediatric medicinal products and medicinal products for rare diseases [74]. The corresponding proposal has just finished the feedback period and will soon come into public consultation. For paediatric medicines four main issues were identified by the European Commission. It was observed that the current system does not lead to an intensified development of products in areas with an unmet therapeutic need within the paediatric population. Furthermore, the incentives are not linked to whether the product is actually placed on the market. This has led to a reduced availability of some products across the Member States. Another drawback of the current provision is that paediatric waivers can be granted based on the condition of a substance's indication even though the substance's mechanism of action seems to be promising in other paediatric conditions. And last but not least, the European Commission acknowledges that the process of applying for SPC extensions

for pharmaceutical companies is bureaucratic and laborious as it requires correspondence with each national patent office.

In order to tackle these challenges, the proposal of the European Commission includes four potential options. The first option is to restrict the granting of an SPC extension to the actual placing of a product on the market in all Member States and to a timely completion of a PIP. This could be accompanied by an improvement of the PUMA. Another option is to grant SPC extensions only to those products that cover an unmet need in the paediatric population. Furthermore, the introduction of an additional reward is considered for products that address an unmet clinical need for children. This reward could be granted in addition to an SPC extension for the completion of a PIP. The last option also includes a new reward for products that cover an unmet clinical need. But in the last option this new reward would replace the current provision of SPC extensions.

The discussion about a revision of the paediatric regulation is overdue even though some important aspects are missing in the current proposal. First of all, it is appreciated that the focus is shifting over to unmet clinical needs instead of rewarding a 'random' paediatric use. Unfortunately, SPC extensions still plays a role as rewards for PIP completion in some of the discussed options. This would disadvantage (new pharmaceutical forms of) known active substances as their patents usually do not qualify for an SPC. A modification of the paediatric regulation should therefore ensure that granted rewards equally apply to products irrespective of their type, i.e. new substances or known substances. Therefore, the Commission's option considering new types of rewards should be preferred. Alternatively, products that are not covered by patents qualifying for an SPC could be exempted from the obligation for a PIP. Whereas this alternative would be against the aim to strengthen paediatric medicines development.

The most obvious shortcoming of the Commission's proposal is that it skips the chance for a holistic approach to address significant unmet clinical needs in the EU. Supporting the development of medicines for the paediatric population and for rare diseases is of utmost importance and should be of high priority. However, in contrast to that, other unmet clinical needs have been neglected for years from a regulatory perspective. This has in parts led to an

unbalanced development. For example, in the field of neurology adequate pharmaceutical forms of known active substances are missing to treat acute convulsive seizures in adults if no intravenous access is available (e.g. intranasal/buccal midazolam or intranasal lorazepam) [75, 76]. In these cases German guidelines even recommend *Buccolam* - a product explicitly developed under the paediatric regulation - to be used *off label* in adults [76]. This example demonstrates the gap between the important regulatory promotion of paediatric drugs on one side and the poor regulatory incentives for innovations of new pharmaceutical forms of known active substances in non-paediatric and non-rare disease indications on the other side.

Considering the above, a combined holistic approach for paediatric and adult unmet clinical needs in the EU should strongly be preferred. This is neither meant to undermine the importance of developing paediatric medicines nor to play innovations in adults and paediatrics off against each other. Instead, a combined approach could make use of synergistic effects that arise from a common reward and incentives system for medicinal products that cover unmet clinical needs.

It is acknowledged that regulatory aspects are just one part of the entire spectrum. The decision of pharmaceutical companies to develop medicinal products is not only based on regulatory considerations but also on pricing and reimbursement issues which are not being discussed in this thesis. Especially in cases where established medicinal products are used *off label* to cover an unmet need, it has to be assumed that the *off label* use of these products partly continues even if a dedicated new pharmaceutical form would be developed addressing this particular need. This effect will be stronger the higher the price for the new pharmaceutical form would be. It demonstrates that new pharmaceutical forms of known active substances compete pricewise with the established products of that substance, even if the new pharmaceutical form would address an unmet clinical need. This might hinder pharmaceutical companies to invest in the costly development of new pharmaceutical forms.

Consequently, when trying to strengthen the development of medicines that address unmet clinical needs not only appropriate regulatory measures have to be considered but also modifications to the pricing and reimbursement policies may be required. However, the challenge with this is to promote innovations but to keep an affordable price level of medicines

throughout the EU. This is one of the main goals of the current European Commission's pharmaceutical strategy [19]: *"fulfilling unmet medical needs and ensuring accessibility and affordability of medicines"*.

8 Summary

The European regulatory landscape offers some good opportunities for new pharmaceutical forms of known active substances. Current regulations allow MAAs to rely on reference medicinal products or on published data. This reduces developmental efforts for new products. Furthermore, a wide range of scientific guidelines relevant to the development of new pharmaceutical forms of known active substances are available, reflecting current scientific knowledge and the expectations of regulatory authorities. This helps applicants to align their development processes and make them more efficient.

However, there are some challenges for new pharmaceutical forms of known substances in the EU. One of the most important is the limited eligibility for data exclusivity or market protection even if the new pharmaceutical form comes with a significant clinical benefit. There are only two options to achieve additional regulatory protection for new pharmaceutical forms of known active substances, both of which fall to short: the introduction of a new indication according to Article 10(5) of Directive 2001/83/EC and the use of the PUMA according to Chapter 2 of Regulation (EC) No 1901/2006. Whereas the shortcomings of the paediatric regulation have already been acknowledged and proposals for a revision are ongoing, no attempts are made to improve the incentive and reward system for new medicinal products of known substances that cover an unmet clinical need in adult non-rare disease indications.

A proposal is made for an holistic approach harmonising the reward and incentive system for all products covering unmet clinical needs in the EU irrespective of the target population. This does not mean to give up the specific fostering of the development of paediatric medicines but to integrate it into the larger context of unmet clinical needs. Care should be taken that

incentives and rewards granted in such a system equally apply to products irrespective of their type, i.e. new vs. known active substances.

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Erklärung

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

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Ort, Datum Unterschrift