Different Salts of a Drug Substance –

Comparison of Regulatory Pathways in the EU and USA

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Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
AUC	Area under the Curve
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BfArM	Bundesinstitut für Arzneimittel
BPCA	Best Pharmaceuticals for Children Act
C_{max}	Maximum Concentration (Pharmacokinetics)
CA	Competent Authority
CEP	Certificate of Suitability with the European Pharmacopeia
CFR	Code of Federal Regulations
CHMP	Committee of Human Medicinal Products
CMS	Concerned Member State
CPMP	Committee for Proprietary Medicinal Products
CYP2C19	Cytochrome P450 enzyme subfamily
DCP	Decentralized Procedure
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug and Cosmetics Act
GBA	Gemeinsamer Bundesausschuss
HMA	Heads of Medicine Agencies
IP	Intellectual Property
IR	Immediate Release
LOEL	Lowest observed effect level
Log P	Logarithm of Partition Coefficient (Oil-Water)
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MRP	Mutual Recognition Procedure
NDA	New Drug Application
NICE	National Institute for Health and Care Excellence
NOEL	No Effect Level
NSCLC	Non-small Cell Lung Cancer

OTC	Over-the-Counter
PAES	Post-approval Efficacy Study
PAR	Public Assessment Report
PFI	Powder for Injection
PIL	Package Insert and Label
PIP	Pediatric Investigational Plan
pK	Negative Logarithm of Acid or Base Dissociation Constant
RH	Relative Humidity
RLD	Reference Listed Drug
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
t_{max}	Time at which C_{max} is Reached
WHO	World Health Organization

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1. Introduction

Many small molecule drug substances are developed as a salt, primarily to improve chemical stability and to increase aqueous solubility. During development of a novel medicinal product, there are often several salt forms under evaluation. Selection of the final salt form depends on a variety of critical quality attributes, such as oral availability, stability, solubility, log P (octanol-water partition coefficient), pK value (dissociation constant), hygroscopicity, existence of polymorphic forms, particle size and more. [1]

Generic companies routinely screen and re-evaluate salts of a drug substance in an already approved medicinal product. In some cases, the generics company may decide to develop a new salt form of the original drug substance. Furthermore, the originator might choose to switch to another salt, e.g. as line extension. These different salts fall within the category of *pharmaceutical alternative* (see below for definition). A pharmaceutical alternative might be developed due to different reasons:

(i) *patent considerations:* if the pharmaceutical alternative is not (any longer) covered by patents of the original medicinal product and if the data protection period (see Section 3.3) has elapsed, the pharmaceutical alternative might allow the generics company a faster entry into the market than with the originator's salt;

(ii) *life cycle management:* improved solubility, dissolution and/or stability of a pharmaceutical alternative could lead to an improved product;

(iii) *line extension:* novel pharmaceutical dosage form and/or route of administration due to altered bioavailability could lead to a different dosage form such as prolonged release or different routes of administration.

If a substance is to be developed as pharmaceutical alternative of an already approved salt, there are various regulatory strategies to achieve marketing approval; these strategies are different in the EU and in the USA. For orally applied medicinal products, bioequivalence (BE) plays a significant role as the basis to establish therapeutic equivalence. It has bee]n questioned whether a pharmaceutical alternative should be approved solely based on BE. [2, 3, 4] Sometimes, different salts of an active substance exhibit different solubility and consequently show a different pharmacokinetic behavior. Examples of this are diclofenac potassium and sodium salt (see Section 4.4) or metoprolol tartrate and succinate salt. [5] Concerns have been raised in case a salt switch would be initiated for a drug with a narrow therapeutic window [2], even though for such compounds tighter limits for bioequivalence have to be applied. [6]

BE is of minor importance for medicinal products administered non-orally (e.g., topically or via inhalation), but it can also be used to support therapeutic equivalence and differences in salt properties can be of relevance. For intravenously applied medicinal products, 100% bioavailability is assumed and a BE study is not required. In any case, different salt properties can lead to a different medicinal product.

It is the objective of this Master thesis to review and discuss the approval strategies in the EU and USA for medicinal products which are systemically administered and which contain different salts. Based on selected examples, the discussion addresses the question whether the different regulatory approval routes are justified and whether concerns regarding generic substitution are justified. Recommendations are provided for specific regulatory requirements in case a pharmaceutical alternative is developed as generic or hybrid application, respectively.

2. Definitions

2.1. Pharmaceutical Equivalence

The definition of *pharmaceutical equivalence* is provided in the EMA Guideline on bioequivalence [6]:

> "Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage form that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to faster or slower dissolution and/or absorption."

Here, the term *same active substance* is not defined, i.e. it is not clear whether the definition comprises different salts, esters etc. of the same substance. However, it is explicitly stated that bioequivalence is not implied.

While in the EU, pharmaceutical equivalents are defined based on technical pharmaceutical parameters such as strength and dosage form, in the USA the definition of a pharmaceutical equivalent is much more narrow and implies bioequivalence as follows [7]:

> "Drug products are considered pharmaceutical equivalents if they contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration (e.g., chlordiazepoxide hydrochloride, 5 mg capsules). Pharmaceutically equivalent drug products are formulated to contain the

> same amount of active ingredient in the same dosage form and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling."

An even more explicit definition is provided in 21 CFR 320.1 [8]:

> "Pharmaceutical equivalents means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e. , the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates."

In summary, in the EU the term pharmaceutical equivalent is defined independent of bioequivalence, whereas in the US bioequivalence is implied in the definition.

2.2. Pharmaceutical Alternative

The definition of a pharmaceutical alternative is provided in the EMA Guideline on Bioequivalence:

> "Pharmaceutical alternatives are medicinal products with different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active moiety, or which differ in dosage form or strength." [6]

The definition of a pharmaceutical alternative in the USA is similar to that in the EU and can again be found in two different sources. In the Orange Book it is stated:

> "Drug products are considered pharmaceutical alternatives if they contain the same therapeutic moiety, but are different salts, esters, or complexes of that moiety, or are different dosage forms or strengths (e.g., tetracycline hydrochloride, 250mg capsules vs. tetracycline phosphate complex, 250mg capsules; quinidine sulfate, 200mg tablets vs. quinidine sulfate, 200mg capsules). Data are generally not available for FDA to make the determination of tablet to capsule bioequivalence. Different dosage forms and strengths within a product line by a single manufacturer are thus

> pharmaceutical alternatives, as are extended-release products when compared with immediate-release or standard-release formulations of the same active ingredient.” [7]

In 21CFR 320.1 the following definition is found:

> “Pharmaceutical alternative means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates.” [8]

2.3. Bioequivalence

The term suggests that two compounds are biologically equivalent; for orally available medicinal products, it is fundamental for establishing therapeutic equivalence between two medicinal products.

In the EMA guideline on bioequivalence (BE), the following definition is found:

> “Two medicinal products containing the same active substance are considered bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits.” [6]

Guidance on demonstrating BE between two immediate release oral dosage forms (tablets, capsules, orodispersible tablets, oral solutions) as well as immediate release non-oral dosage forms with systemic action (e.g., rectal formulations) is described in the respective EMA guideline. [6] Here, it is also stated that for parenteral solutions, BE studies are generally not required. For modified release formulations, guidance on BE studies is provided in reference [9], for fixed combinations the BE requirements are described in reference [10].

In the USA, BE is defined as found in 21 CFR 320.1:

> “Bioequivalence means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” [8]

In summary, both in the EU and in the USA, BE is defined very similar and based on pharmacokinetic parameters. In principle, it can be established both between pharmaceutical equivalents and alternatives.

2.4. Therapeutic Equivalence and Generic Drug

In the EU, the idea of therapeutic equivalence is contained in the definition of a generic medicinal product, contained in Directive 2001/83/EC Article 10(2)(b):

> "'Generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy." [11]

This means that if BE is demonstrated, therapeutic equivalence can be concluded even for a pharmaceutical alternative, e.g. for another salt than that in the approved product. In this case, the pharmaceutical alternative could become a generic medicinal product. A different salt of an active substance can be registered as a pure generic substance (Article 10(2)), as a hybrid (Article 10(4)) or as a completely new application (Article 8). [11]

For the USA, an explicit definition of therapeutic equivalence can be found in the Orange Book:

> "Drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling." [7]

Based on this definition, it is not possible in the USA to register a different salt of an already approved drug substance as a generic medicinal product.

In summary, there are significant differences between the EU and the USA in the understanding of therapeutic equivalence. In the EU, therapeutic equivalence is primarily based on the demonstration of bioequivalence; in the USA, pharmaceutical equivalence is required in addition to BE.

3. Results

3.1. Regulatory Pathways in the European Union

In the EU, Directive 2001/83/EC outlines three different approval pathways for a pharmaceutical alternative: a generic application, a hybrid application or a full application. They are visualized in Figure 1 and described in the subsequent sections.

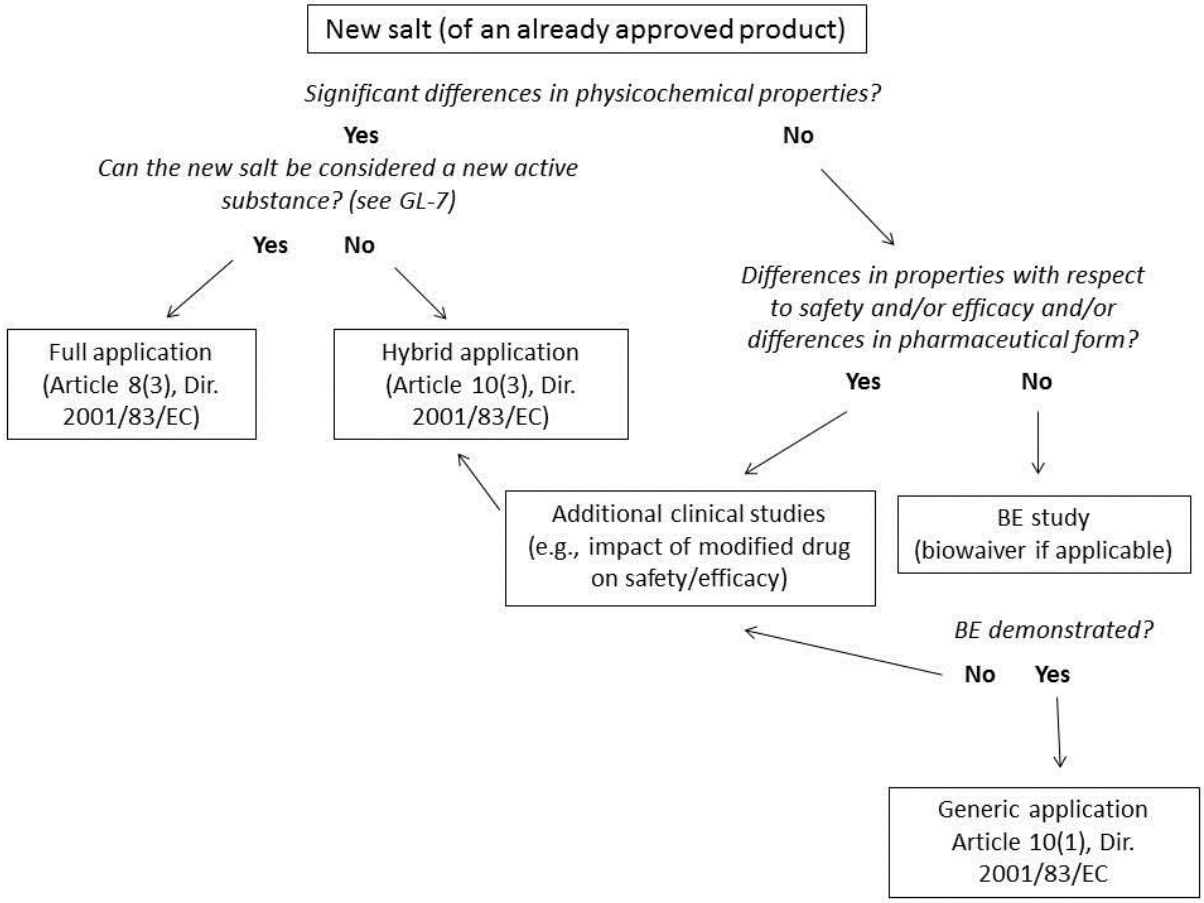

Figure 1: Regulatory Pathways in the EU for a New Salt

3.1.1. Generic Application

A pharmaceutical alternative of an active substance which is already marketed in a medicinal product can be approved in a generic medicinal product according to Article 10(1) of Directive 2001/83/EC, provided that the new medicinal product has (i) the same qualitative and quantitative composition in active substance(s) as the reference, (ii) the same pharmaceutical form and (iii) bioequivalence has been demonstrated. [11] Bioequivalence is to be demonstrated as outlined in the respective guideline for immediate release drug

products [6], for modified release drug products [9] or for fixed combination products [10], respectively.

The definition of a generic medicinal product (see Section 2.4) states explicitly that a different salt in a generic medicinal product is considered the *same active substance* as the reference medicinal product *only* if it does not differ "…. significantly in properties with regard to safety and/or efficacy". According to NTA, Vol. 2A, Chapter 1, evidence should be provided that "…there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could significantly change the safety/efficacy profile." [12] Thus, it is the responsibility of the applicant to generate data to address the above cited criteria. The competent authorities will decide on a case-by-case basis whether a different form of an active substance is to be considered as a new active substance. [12]

If the applicant comes to the conclusion that there are significant differences between the new salt and the original salt, "… additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorized active substance must be supplied by the applicant." [11] Notably, there is no specific guidance on which additional data are to be provided. If additional data "…cannot establish the absence of a significant difference with regard to safety or efficacy…." [11] a generic application is not possible.

Then, two options arise: (1) the applicant must "submit the results of appropriate pre-clinical tests and clinical trials in accordance with the requirements of Article 10(3)" [12], i.e. a hybrid application is required (see Section 3.1.2). (2) The competent authorities will evaluate on a case-by-case basis whether a different form of the active substance is to be regarded as a new active substance. [12] In this case, an application according to Article 8(3) of Directive 2001/83/EC would follow (see 3.1.3).

3.1.2. Hybrid Application

According to Article 10(3) of Directive 2001/83/EC, there are instances where "the medicinal product does not fall within the definition of a generic medicinal product … or where bioequivalence cannot be demonstrated." [11] Examples could be "changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration". [11] In these situations, additional pre-clinical and clinical data are to be provided with the objective to allow bridging from data of the original medicinal product to the new product (e.g., new salt). Further guidance on the required additional data can be found in Annex II of reference [12]. For example, if a product with a different strength or with suprabioavailability is to be developed, clinical data on bioavailability might suffice. However,

if a different route of administration is selected, most likely additional clinical data on safety and efficacy need to be provided.

While a generic medicinal product cannot become a reference medicinal product for other generics, a medicinal product approved according to Article 10(3) of Directive 2001/83/EC can be a reference medicinal product for other generics. For example, a topical cream approved according to Article 10(3) can refer to some (pre)clinical data of the originator's immediate release tablet; if approved, another company can develop a generic topical cream with reference to the topical cream approved first. This will be exemplified with diclofenac in Section 4.4.

3.1.3. Full Dossier

In case that an alternative salt of an already existing medicinal product differs significantly with respect to safety and/or efficacy data, this new substance might be considered a new active substance as outlined in Annex I of reference [12] As a consequence, a full dossier according to Article 8(3) of the Directive 2001/83/EC has to be submitted. For example, Voltarol® is a diclofenac formulation where a liquid filled capsule of diclofenac potassium is administered; this product has been approved based on a full dossier. [15]

3.2. Regulatory Pathways in the United States of America

Based on the definition of therapeutic equivalence in the USA (see Section 2.4), a generic application is not possible when a different salt is to be used in the new medicinal product. As a consequence, a different salt can only be authorized as NDA (New Drug Application, i.e. full dossier) according to Section 505(b)(2) of the Federal Food, Drug and Cosmetics Act (FD&C Act). [13] This path resembles the EU's hybrid application and will be outlined in Section 3.2.1.

3.2.1. NDA According to 505(b)(2)

The regulatory pathway according to 505(b)(2) has been added to the FD&C Act in 1984. It permits FDA for approval of an NDA to rely on data not provided by the applicant. [14] Among other options, it allows the development of an "improved generic drug", e.g. using an improved pharmaceutical form or a different salt, modifying the drug substance otherwise, developing a combination product, a new indication or an OTC switch, respectively. Such applications are possible for new chemical or molecular entities in case some of the data has already been generated for another medicinal product approved by FDA.

Similar to the hybrid application in the EU, the driving force of this pathway was the intention to encourage innovation but to avoid duplication of work, especially (pre)clinical studies. This

regulatory route requires more input by the pharmaceutical company than an ANDA, the latter being as much a copy of the reference listed drug as possible. As a reward, a 505(b)(2) application can afford up to 3 years of market exclusivity in case reports of new clinical investigations (other than bioavailability studies) have been submitted. This is an immense incentive, especially considering that an full NDA according to 505(b)(1) will receive at most 5 years of market exclusivity. [16] It has been reported that there are 505(b)(2) products which have been generated with relatively little additional investment for clinical and nonclinical studies and within about three years. [17]

Briefly, the sponsor of a 505(b)(2) application will refer to preclinical and clinical data (including safety data) of an originator. In addition, the sponsor will provide data that allow bridging from the original medicinal product to the newly developed medicinal product, e.g. from an immediate release formulation to a new prolonged release formulation, or from the originator's medicinal product to a new combination product. These bridging data will most likely include data from additional therapeutic studies. However, since the 505(b)(2) application will refer to an already approved medicinal product, there is generally a lower risk of failed development since data on safety, mode of action, drug-drug interaction, metabolism etc. is already available.

The interaction with the FDA is expected to be more intensive than for an ANDA, requiring the respective resources from the sponsor. FDA approval time is shorter. Furthermore, there is a chance for the sponsor to generate new IP, but also the challenge to maintain and defend it.

Formally, the 505(b)(2) is considered an NDA; however, a patent certification (according to 21 CFR 314.50(j)) similar to those required for an ANDA is required.

3.3. Patent and Data Protection Considerations

When a medicinal product involving a different salt of an original medicinal product is to be submitted, it is necessary that relevant patents have expired. The regular patent term is 20 years from filing worldwide. In addition, the data protection period (see below for details) must have elapsed since both the generic and the hybrid application refer to parts of the originator's dossier.

3.3.1. European Union

The data protection period has been set to 8 years after approval of the original medicinal product. The overall market exclusivity period of the original medicinal product is 10 years for medicinal products approved after 30 Oct 2005. [11] For medicinal products approved prior

to 30 Oct 2005 in the EU, the data protection period was 6 or 10 years, depending on the country. The market exclusivity period in the EU can be extended for one additional year in case new data is submitted which results in a marketing authorization in another medical indication. [11] However, this also means that the data protection and market exclusivity periods are applied only once; line extensions (such as an additional indication) do not result in the "reset" of the market exclusivity period. Another option for extended market exclusivity is the approval of a medicinal product in an orphan indication (i.e., condition that affects no more than 5 in 10,000 people in the EU). Here, for a period of 10 years no other application for marketing authorization of a similar product in the respective orphan indication is accepted by the EMA. [18] In case a pediatric investigation plan (PIP) was performed in an orphan indication, the market exclusivity is extended to 12 years. [19]

There is the option to extend the patent term (supplementary protection certificate, SPC) to account for patent time lost due to clinical development. Briefly, the SPC allows to extend the patent term for up to 5 years, depending on the date of marketing approval (overall protection period not to exceed 15 years). This SPC can be extended for another 6 months in case a PIP was performed.

3.3.2. United States of America

The data protection period for a new chemical entity is only five years [16], after that a generic company can file an abbreviated new drug application (ANDA). The ANDA can get approval on the day of patent expiry. In case the applicant has performed clinical studies in children under the BPCA (Best Pharmaceuticals for Children Act), the patent term and data exclusivity for all products containing the respective active substance are extended for an additional 6 months. In case an application according to 505(b)(2) was approved, the data protection period granted can vary from zero to three years (depending on the novelty of the new medicinal drug product). In general, data protection is shorter in the USA compared to the EU, which means that patent protection plays a more significant role than in the EU.

The patent protection period in the USA can be extended for up to 5 years under the Hax-Watchman Act (so-called Patent Term Extension or PTE); however, after approval, a sum of 14 years covering data protection and patent term including extension cannot be exceeded.

3.3.3. Relevance for MAAs on Alternative Salts

Interestingly for generic companies, it is possible that the drug substance of the original medicinal product is still covered by a patent but the data protection period has elapsed. In case that a new salt does not fall under the original patent (i.e., active substance is no longer patent protected), in the EU a generic or hybrid application can be filed for a medicinal product containing the new salt and with reference to the originator's dossier, thus

circumventing the originator's substance patent. Similarly, in the USA an application according to 505(b)(2) would be possible. It will be shown in Section 4 that this route has been selected repeatedly by generics companies. As a consequence for the originator, patent protection of all relevant salts should be of high priority.

Table 1: Data and Patent Protection Terms in the EU and USA

	EU	**USA**
Patent term	20 years	20 years
Additional patent protection / data exclusivity	Up to 5 years SPC (Supplementary Protection Certificate)	Up to 5 years Hatch-Waxman Act
Regulatory protection period	8 +2 years (data protection + market exclusivity)	5 +x years (data protection + FDAs dossier evaluation time)
Sum of maximum total patent protection and/or data protection period after MA	≤ 15 years	≤ 14 years

3.4. Opportunities and Risks in Development of a Different Salt

The development of a different salt pertaining to an already approved medicinal product is characterized by less innovation and overall less development risk compared to a new drug substance. A key incentive for such a development both in the EU and in the USA is the potential chance to circumvent a patent which protects only the approved salt of the medicinal product. Another rationale is to specifically modulate the biopharmaceutical properties to address a specific medical need, e.g. with respect to drug release. Furthermore, in the USA there is the chance to obtain additional market exclusivity in case a sufficiently innovative medicinal product is developed which contains the new salt.

The risks of developing an alternative salt are that additional (non)clinical data need to be generated which might uncover new safety issues. This is also due to the fact that the company which intends to develop the new salt typically does not have access to the complete set of preclinical data of the original medicinal product. Furthermore, determining which additional data is required for approval of a different salt is not a standard situation for a typical generics company with little expertise in preclinical development. There is also the risk that a patent lawsuit will follow once the development of an alternative salt is publicly known.

For the regulatory authorities in the EU there is the challenge to decide on approval of a different salt submitted under Article 10(1) based solely on clinical pharmacokinetics data

(often only one BE study for IR dosage forms), sometimes accompanied by preclinical data. The examples in Section 4 will illustrate that in some cases there is doubt on comparable therapeutic efficacy. This risk is less pronounced in the USA, since here the applicant is required under a 505(b)(2) application to submit more clinical data than just a BE study.

4. Examples

4.1. Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker, relaxing the vascular smooth muscles and thereby reducing blood pressure and reducing chest pain. It was originally developed by Pfizer, marketed as Norvasc®, and it is on the WHO list of essential medicines. The medicinal product was first approved in 1989 in Belgium and in 1992 in the USA. The patent protecting the drug substance amlodipine besylate expired 2004 in Europe and 2007 in the USA. [4]

4.1.1. European Union

In the EU, the original medicinal product containing amlodipine besylate was approved in national procedures; as of August 2010 the medicinal product was approved in 140 countries, including all EU member states. [20] It is marketed under various trade names such as Amlor®, Istin®, Monopina®, Norvasc® and others. Immediate release tablets with a strength of 5 and 10 mg are available, in some countries there exist also 5 and 10 mg capsules. In 2011, the MAH Pfizer requested a referral according to Article 30 of Directive 2001/83/EC with the objective to harmonize the SmPCs and to standardize the tests for assessing the quality of Norvasc® in the EU. As a result of this, a harmonized SmPC was issued by the CHMP and the quality of the substance can now be controlled with a CEP. [20] The first approval of a generic amlodipine besylate in the EU was issued in September 2003. [21]

In the EU, the amlodipine maleate salt is available in several countries and it was approved in Sweden as a generic medicine on Feb 21, 2003, i.e. 7 months prior to the first generic version of amlodipine besylate. The initial approval of generic amlodipine maleate was followed by a Mutual Recognition Procedure (MRP) where the application was also submitted to the German Competent Authority (CA) BfArM as one of the Concerned Member States (CMS). The BfArM initiated a referral according to Article 29, Directive 2001/83/EC, on the grounds of potential risk to public health due to impurities found in the maleate salt (Michael-addition of maleate to the amine group of the active moiety and incompatibility

between lactose and drug substance). [22] In order to qualify these impurities, the generics company had conducted additional toxicological studies which served to demonstrate that there is no change in the safety profile. The CPMP concluded after the referral that (i) bioequivalence was proven, (ii) the additional impurities did not pose a risk during long-term treatment and (iii) the benefit-risk ratio was still positive. Subsequently, the referral was resolved. [22] Thus, the generics company was successful in circumventing the patent protecting the besylate salt and the market exclusivity of this widely used blockbuster drug was cut by seven months.

While the referral and the ensuing discussion revealed some information on what documents were provided by the generics company in order to obtain MA for the maleate salt, a search for public assessment reports (PARs) on any of the generic amlodipine maleate products was not successful. [23, 24]

Furthermore, amlodipine mesylate was approved as a generic medicinal product in September 2003 in Denmark, followed by a MRP. There are several medicinal products with this salt on the market in the EU. [25] In the only PAR available (Amlobet®), reference is made to the FDA Summary Basis of Approval (which is not publicly available) and it is stated that the originator (Pfizer) started its own development with the mesylate salt but changed to the besylate salt later “for commercial reasons”. [26] However, according to a different data source, the development was started with the maleate and not with mesylate. The mesylate salt was evaluated among other salts as alternative to maleate. [27] In the PAR for Amlobet®, additional preclinical studies are described. [26] Since it is the only PAR available, it remains unclear whether the other generics companies performed preclinical studies as well. Based on the information available, it is not obvious why the mesylate salt was developed, but it is assumed that the intention was to enter the market earlier than with the besylate salt (which did not work out).

In Table 2, key characteristics of generic products containing different amlodipine salts are summarized. For both alternative salts, preclinical studies were performed to satisfy the requirements outlined in NTA. [12] All products are IR tablet formulations and were approved based on only one BE study in line with the requirements of the EMA guideline on BE [6] for generic medicinal products. It will be discussed in Section 5.1 whether this is considered sufficient for generic medicinal products based on a different salt.

Table 2: Summary of Generic Amlodipine Salt Formulations in the EU

	Amlodipine Besylate[1)]	**Amlodipine Maleate**	**Amlodipine Mesylate Monohydrate**
Solubility / other properties	Slightly soluble in water [28] BCS class I [29]	Solubility > 1 mg/ml [27], thus BCS class I	Soluble in water [26], thus BCS class I
BE	BE was demonstrated, one study per generic product (see PARs, e.g. [30]	BE was demonstrated [22], no details from PARs available; in the literature, a BE study is described (open-label, randomized, single dose, 2-period cross-over, fasting conditions, n=24 [32])	Bioequivalence was demonstrated in one study (open label, randomized, single dose, 2-period cross-over, fasting conditions, n=24 [26])
Dosage form	Immediate release tablet Immediate release capsule Orodispersable tablet [31]	Immediate release tablet Immediate release capsule	Immediate release tablet
Type of Approval	Article 10(1) of Directive 2001/83/EC, (national approval + MRP), first approval: 09/2003 [21] for IR tablet and capsule	Article 10(1) of Directive 2001/83/EC, (national approval followed by MRP), first approval: 02/2003 [22]	Article 10(1) of Directive 2001/83/EC (national approval followed by MRP) First approval: 09/2003 [25]
Justification of essential similarity	No additional preclinical studies One clinical BE study per generic product	Additional preclinical data (no details available) were generated to demonstrate (i) that there is no change in the safety profile of maleate salt compared with original product and (ii) to qualify new impurities specific to the maleate salt.[22]	Single dose and repeat dose toxicity study comparing mesylate and besylate salt (rats, 4 weeks). Same NOEL and LOEL for both salts, comparable effects. [26]
Comments	n/a	In the summary report of the referral, the pharmaceutical development was criticized (not state of the art) and the new impurities were considered foreseeable and avoidable. It was also criticized that the maleate salt was selected solely due to patent considerations. [22]	Human BE data and rodent toxicology studies comparing mesylate and besylate salt were considered sufficient “evidence that there is no change in the PK of the moiety, pharmacodynamics and/or in toxicity which could change the safety/efficacy profile.” [26]

[1)] Counter ion identical to original medicinal product

4.1.2. United States of America

The amlodipine besylate salt was approved by the FDA in July 1992 and it is presently marketed in the USA as Norvasc® by Pfizer in 2.5, 5 and 10 mg dose strength (equivalent to base), as immediate release tablets for oral use. According to Pfizer, the majority of preclinical and clinical studies submitted to FDA were performed with the maleate salt. During the development, Pfizer switched to the besylate salt due to quality concerns (stability, pharmaceutical manufacturing). [33] Consequently, the NDA dossier submitted by Pfizer to the FDA contained data demonstrating BE between the maleate and besylate salt and to allow bridging of development data, preclinical safety data on both the maleate and the besylate salt as well as clinical efficacy studies with both salt forms.

On Oct 31 2003, FDA approved AmVaz® (Dr. Reddy's Laboratories), the amlodipine maleate salt under Section 505(b)(2) of the FFDC Act (N021435). It was assumed by Pfizer [33] that Dr. Reddy's Laboratories had referred to data on the maleate salt submitted by Pfizer in the frame of their besylate NDA. Therefore, this FDA approval was followed by a series of legal disputes where Pfizer alleged that FDA had erroneously referred to safety and efficacy data generated with the maleate salt and submitted by Pfizer with their original NDA. [33] In this context, Pfizer raised doubts that FDA's interpretation of 505(b)(2) as laid out in the FDA draft guideline [14] is in line with the intention of the FD&C Act's drug approval provisions. [33] Specifically, Pfizer considered their data on the maleate salt in their NDA on the besylate salt as Pfizer's proprietary information (trade secret) that cannot be used to approve Dr. Reddy's maleate salt. According to Pfizer's understanding of the 505(b)(2), Dr. Reddy's can only rely on data pertaining to the besylate salt. Furthermore, Pfizer alleged that its patent on the maleate and besylate salt was infringed. [34] In early 2004, the FDA put the approval on hold due to the patent suit, not allowing Dr. Reddy's to market the product prior to 2007. From the publicly available data it is not clear if and how the dispute between Pfizer and FDA on the interpretation of an application under 505(b)(2) was settled. AmVaz® was discontinued in the USA, presumably since its main attractiveness was the circumvention of the Pfizer patent. Even though an application under 505(b)(2) can result in additional market exclusivity, this was not the case with AmVaz®, since no substantial improvement was associated with this pharmaceutical alternative.

In the USA, there are various generic amlodipine besylate salts approved. [7] All are considered therapeutically equivalent to each other and to the reference listed drug (RLD). However, approval summaries are not published, therefore no evaluation was possible on the information to establish essential similarity.

There was also an orally disintegrating tablet of amlodipine besylate which was submitted by Synthon Pharmaceuticals as an application under 505(b)(2) [35] but later discontinued.

According to the approval summary review of the FDA, bioequivalence of this formulation to the RLD was shown (single dose in vivo study in healthy subjects and food effect study). Although this was also an NDA according to 505(b)(2), no new exclusivity was awarded to this application.

4.1.3. Summary and Conclusion

Both in the EU and in the USA, the incentive for introducing the maleate salt was to circumvent the original Pfizer patent. This was done with some success in the EU (7 months earlier market entry for the maleate salt), but not in the USA. Possibly, the rationale for the introduction of the generic mesylate salt in the EU was also circumvention of the besylate patent.

In the EU, both for the maleate and mesylate salt, additional preclinical data were submitted, in line with the regulatory requirements. [12] Furthermore, in the EU one BE study was sufficient for the IR dosage form. Both in the USA and in the EU, two studies (one BE, one food effect) were reported for the orodispersible tablet. There is no information available on BE studies of the generic besylate salt in the USA.

At the time of accessing the HMA database, 37 products based on amlodipine mesylate [25] and 34 products based on amlodipine maleate were listed. [23] These numbers indicate that the alternative salt products have found a niche on the generics market and that pharmacovigilance and efficacy observations covering more than 10 years have not revealed safety signals deviating from the original salt. Of all products containing a different salt, there was only one PAR accessible for the mesylate salt (Amlobet®) and none for the maleate salt. Therefore, it is not possible to evaluate in detail what specific information was provided by the generics companies to demonstrate essential similarity. Moreover, it is not possible to determine how many of these applications included new preclinical data.

4.2. Clopidogrel

The antiplatelet agent Clopidogrel (Plavix® by BMS and Sanofi) was approved in the USA in November 1997 [7] and in the EU in July 1998. [36] It is an orally available small molecule of the thienopyridine class, indicated for the prevention of atherothrombotic events in adult patients suffering from myocardial infarction or from acute coronary syndrome. [37] The product is on the WHO list of Essential Medicines and the drug substance has been classified as BCS class 2. [38]

Clopidogrel is a prodrug which undergoes several parallel metabolic pathways. Primarily, it is hydrolysed pre-systemically, i.e. in the gastro-intestinal tract, to the inactive metabolite

clopidogrel carboxylic acid (about 2000-fold increased concentration compared to clopidogrel). In a parallel pathway, the active metabolite clopidogrel thiol is formed in the intestine and liver by the CYP2C19 enzyme isoform. [39, 40] At the time of approval of the innovator drug, there was no reliable bioanalytical method available to monitor either the prodrug clopidogrel or – even more relevant – the active metabolite clopidogrel thiol. Therefore, all PK information at that time was based on plasma levels of the carboxylic acid, i.e. the inactive metabolite. In subsequent years, bioanalytical methods improved and allowed measurement of the parent drug clopidogrel. [40] As a consequence, for the upcoming approval of generic clopidogrel products, including different salts, the EMA stated that a switch was required from measuring the carboxylic acid to measurement of the clopidogrel (prodrug) during BE studies. [40] With the improved bioanalytical methods, more information became available on food effect [41] as well as on drug-drug interactions with proton pump inhibitors affecting the bioavailability of clopidogrel. [42] It was demonstrated that in the fed state, the bioavailability of clopidogrel measured as the prodrug increased to 500-600%, while the clopidogrel carboxylic acid increased only by 10-20%. [41] This can be explained with reduced hydrolysis in the fed state, leading to an increased clopidogrel concentration available for absorption. As a consequence, more prodrug can be converted by CYP2C19 to the active clopidogrel thiol. These observations led to the question whether a BE study in the fasted state is sufficient, or whether BE should also be evaluated in fed conditions. Normally and according to the Guideline on investigation of BE, in the EU only one BE study in the fasted state is required "… as this is considered to be the most sensitive condition to detect a potential difference between formulations." [6] The Pharmacokinetics Working Group at the EMA stated that the solubility of the different clopidogrel salts is of importance. [40] However, at low pH all clopidogrel salts have a high solubility, leading to similar hydrolysis extent. [43] As a consequence, similar behavior of all clopidogrel formulations, irrespective of the salt, would be expected. The PK working group concluded that no additional fed state BE study is required. The evaluation of the different salts (see Table 3) shows that solubility and dissolution at different pH values were carefully discussed by all applicants.

4.2.1. European Union

In the EU, generic clopidogrel formulations with various salts have been approved: hydrogen sulfate, besylate, hydrochloride (HCl), hydrobromide (HBr), free base and napadisylate. An overview of patent and data protection time lines is presented in Figure 2, important aspects of the different salts are discussed in the following and the salts are summarized in Table 3.

The time lines in Figure 2 illustrate that in Europe, several salts were not covered by the original patent and/or the original patent was not filed in all countries. Thus, it was possible to

file generic applications at the end of the data protection period, up to four years prior to patent expiry. Note that the market exclusivity of the original product was extended by one year after adding a second indication (patients suffering from acute coronary syndrome).

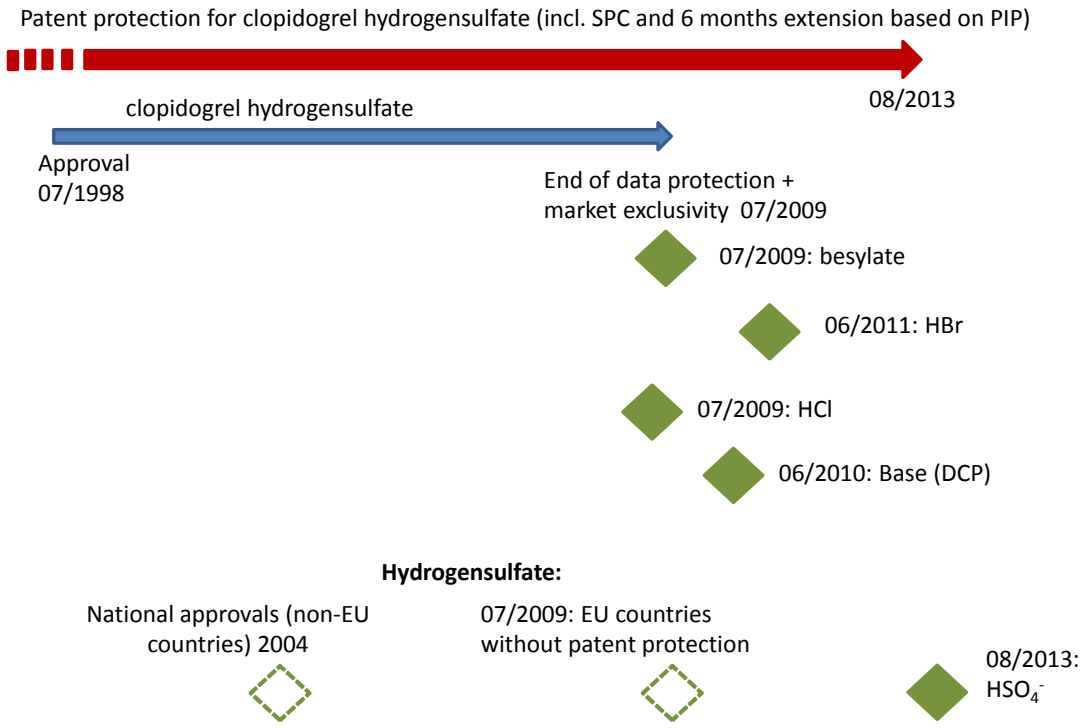

Figure 2: Time Lines of Clopidogrel Salts in the EU [44] Green diamond: date of earliest approval.

Whereas normally in the EU only one BE study (fasted state) is required, in the case of generic clopidogrel formulations (containing either the hydrogen sulfate or even another salt) there are several examples where more than one study was performed (see Table 3). This appears to be attributed to the complex bioanalytical situation: instead of the active clopidogrel metabolite, either the inactive metabolite or parent is measured. This makes it even more complicated to assess whether demonstration of BE between two different salts allows to conclude that the active metabolites will behave therapeutically equivalent.

The besylate and HCl salt were the first generic clopidogrel products (see Figure 2). For the HCl salt it was considered necessary to provide new toxicological studies, i.e. an acute and chronic (13 weeks) toxicity study in rats. [45] Furthermore, the genotoxicity test battery was repeated with the HCl salt. [45] There are several products based on clopidogrel HCl salts approved (search on HMA and EMA website). For all products, the same nonclinical studies are reported. However, the phrasing in all available PARs is identical, which suggests that the applicants may have referred to the same preclinical study. With respect to the besylate

salt, the CHMP raised concerns that a salification agent such as besylate might impact the anti-aggregation effect of platelets. [46] The applicant argued that the besylate salt undergoes dissociation and fast elimination from the body. Furthermore, the applicant evaluated literature data on other besylate salts on the market and did not find any indication that the besylate counter ion poses a safety risk. Similarly to the HCl salt, there are several products on the market containing the besylate salt. In all available PARs, the CHMP concern on the besylate counter ion and the applicant's literature based argument are found.

For the free base and napadisylate no information on additional preclinical studies was found. It appears that the HCl and besylate salt raised concerns since they were the first generic applications.

The salts listed in Table 3 are all of comparable high solubility (especially at low pH) and of good crystallinity with the exception of the free base. The latter is described as non-crystalline and chemically instable; specifically, it has been described that it is susceptible to racemization and hydrolysis. [47] As a consequence, the pharmaceutical product was formulated with the antioxidant butylated hydroxyl anisol which led to an Article 29 referral during the authorization process. [48] The observations on significantly different physicochemical properties are corroborated by a report showing a correlation between the switch from clopidogrel hydrogen sulfate to free base and concomitant less efficient inhibition of platelet activation. [49] Since high platelet reactivity is associated with a significantly higher incidence of ischemic events, such observations are extremely important. The authors concluded that in post-marketing surveillance of generic clopidogrel drugs would be required.

In addition, concerns have been raised in European countries on the substitution of Plavix® with a generic product. For example, the Austrian Cardiology Society (ÖKG) recommends not to substitute Plavix® with a generic product for prevention of stent thrombosis, since stent thrombosis is associated with high morbidity and mortality and any deviation from the well-known original product is considered an unnecessary risk. [50] A key argument of the ÖKG is that there are no clinical data on efficacy and safety of generic clopidogrel products; the bioequivalence studies are not considered sufficient. Contrary to this statement, the Austrian CA recommends generic substitution, primarily with the argument that the salts would dissociate and be converted into the active metabolite. Considering the good solubility of all clopidogrel salts, it is not likely that different salts will have different pharmacodynamics effects. [51] However, this is contradicted by the finding that clopidogrel hydrogen sulfate is BCS class 2. [38] It is well known that for BCS class 2 compounds the drug solubility affects bioavailability and that drug solubilisation is the rate limiting step in the drug absorption process.

In order to increase the confidence of medical professionals in the decision of CAs, the publication of PARs would be very helpful. In special cases, for example drugs with a narrow therapeutic window or in an indication with high mortality, it might also be helpful to involve the medical community into the scientific evaluation of an application. For example, a list of questions might be generated by the organization of medical professionals and forwarded to the applicant. Approval of a generic medicinal product is of little use if the medical community counsels against its use, as in the case of the ÖKG and clopidogrel products.

Table 3: Summary of Generic Clopidogrel Salt Formulations in the EU[1]

	Clopidogrel Hydrogen sulfate[2]	**Clopidogrel Besylate**	**Clopidogrel HCl**	**Clopidogrel HBr**	**Clopidogrel Base**	**Clopidogrel Napadisilate**
Solubility / other proper-ties	pH 1.2: ca. 220 mM, pH 4.5: ca. 95 mM [43] Several polymorphic forms are known	pH 1.2: ca. 180 mM pH 4.5: ca. 40 mM [43] Only one polymorphic form	pH 1.2: ca. 250 mM pH 4.5: ca. 80 mM [43]	pH 1.2: ca. 160 mM pH 4.5: ca. 70 mM [43] Thermally instable monohydrate	pH 1.2: similar to salts water: 3.4 µM [43] Oily, viscous, unstable substance, pKa = 4.5 [43]	No solubility information
BE	Two BE studies, one measuring clopidogrel (n=97) and one measuring clopidogrel acid (n=24), one PK study to assess intra-subject variability of Plavix®.[52]	One BE study (n=46) [46]	One BE study (n=92) [45]	Four studies: compare (i) two HBr formulations with reference, (ii-iii) proposed product vs. reference measuring clopidogrel or clop. carboxylic acid , (iv) evaluate intra-subject variability [53]	No access to national PAR	No access to national PAR
Dosage form	Immediate release tablet	Immediate release tablet	Immediate release tablet	Immediate release tablet	Immediate release tablet	Immediate release tablet
Type of Approval, date of first approval	Centralized procedure, Article 10(1) 07/2009 [52] (in countries where no patent extension was applicable) 08/2013 (major EU countries)	Centralized procedure, Article 10(1) 07/2009 [46]	Centralized procedure, Article 10(1) 07/2009 [45]	Centralized procedure, Article 10(1) 06/2011 [53]	Two DCP, both with Germany as RMS, followed by Article 29 referral [48] 06/2010 [48]	National procedures in Europe [54]

[1] For centrally approved products, the EPAR of the first approved product was evaluated.
[2] Counter ion identical to original medicinal product
[3] Study design according the BE guideline (randomized, open label, 2-period cross-over, fasting if not noted otherwise)

	Clopidogrel Hydrogen sulfate[2]	**Clopidogrel Besylate**	**Clopidogrel HCl**	**Clopidogrel HBr**	**Clopidogrel Base**	**Clopidogrel Napadisilate**
Justifi-cation of essential similarity / other studies	Discriminating dissolution method at pH 1 was developed; dissolution profiles were compared at 3 different pH values; 3 generics and 2 original batches were compared w.r.t. impurities, enantiomeric purity.	Essential similarity was justified based on literature data; no new nonclinical data submitted [46]	Acute, 13-weeks repeat dose toxicity studies and genotoxicity studies compared HCl and HSO_4 salt. PK, dissolution (pH 1.2, 4.5, 6.8), rate of AEs and other clinical data were compared.	No new nonclinical studies	No information	Efficacy and tolerability in Korean patients described [54]
Comment	Marketing possible only after expiry of SPC (+6 months extension based on PIP) which was 08/2013	Some products based on besylate salt withdrawn, some are still on the market	Some products based on HCl salt withdrawn, some are still on the market	Product withdrawn	Product withdrawn	n/a

4.2.2. United States of America

The reference listed drug is Plavix® (clopidogrel hydrogen sulfate), which was approved in November 1997. Various other generic products comprising hydrogen sulfate salts are listed in the Orange Book, the earliest approval was in May 2012. [7] There are no other salts than hydrogen sulfate listed; this implies that the patent protecting clopidogrel did not allow other salts of the substance to be developed under a 505(/b)(2) NDA. When the patent expired, there was no longer an incentive to develop an alternative salt.

Nevertheless, there is a report on an increase of acute and subacute stent thrombosis in a USA hospital following administration of generic clopidogrel containing the same salt, i.e. hydrogen sulfate. [55] The authors report an unexpected, more than twofold increase in stent thrombosis at a single center in the first 80 days of generic clopidogrel use compared to the same time period immediately prior to generic clopidogrel use. Even though no causality could be found, such observations require attention and further pharmacological evaluation of generic products. There is no follow-up literature on this topic, leading to the conclusion that these observations were somehow resolved. Here, a proper approach would have been a quality complaint, leading to an in-depth evaluation of used batches of drug product and substance. Since only a relatively small number of patients was under investigation, only a large-scale, post-approval safety study could have elucidated a possible causality.

4.2.3. Summary and Conclusion

Clopidogrel is an example where different salts have shown bioequivalence based on the parent drug (prodrug). In the EU, this allowed to market these salts as generic medicinal product with Plavix® as reference. At the time when generic medicinal products were evaluated for approval it was technically possible to measure the parent; it is assumed that equivalent quantities of parent will lead to equivalent quantities of active metabolite.

The main driving force for development of the different salts was the potential to circumvent the originator's patent for clopidogrel hydrogen sulfate.

4.3. Pemetrexed

Pemetrexed is a chemotherapeutic compound which is intravenously applied and acts as a folate antimetabolite. It is used in the treatment of malignant pleural mesothelioma [56] and non-small cell lung cancer (NSCLC). [57] The original medicinal product was developed by Eli Lilly and Company. It was approved in the EU in September 2004 and in the USA in February 2004 (Alimta®).

The drug substance is a disodium salt that exists in two crystalline hydrate forms and is freely water soluble (>90 mg/ml at 20°C, pH range 6 to 10). The hydrate form of Alimta® is the heptahydrate. [58] Its formation is controlled by water content during production. Based on a molecular weight of 427.4 g/mol, the heptahydrate form corresponds to a theoretical water content of 22.8%. Stability over 36 months has been demonstrated under long term storage conditions (25°C, 60%RH). [59] The finished product is a lyophilized powder which contains the active substance, mannitol and HCl or NaOH to adjust the pH during manufacturing. The powder is reconstituted with 20 ml NaCl (isotonic) prior to intravenous application. Manufacturing of the product takes place under aseptic conditions and in absence of oxygen, since the substance is susceptible to oxidative degradation. [59]

4.3.1. European Union

In September 2015, first generic pemetrexed products have been approved in the EU based on Article 10(1) of Directive 2001/83/EC. In all generic pemetrexed products (except Pemetrexed Lilly), the disodium hemipentahydrate is used, since the heptahydrate is still under patent protection. [60] It is also freely soluble in water but it appears to be less stable than the heptahydrate, since long-term stability data of the drug substance were generated at 2-8°C. [61, 62, 63, 64] However, the applicants were all able to generate a drug product which is stored and handled comparably to the original medicinal product (see Table 4). BE studies were not required since the finished product is administered intravenously in the same concentration as the original product and 100% bioavailability is assumed.

In January 2016, a pemetrexed medicinal product (Armisarte®) was centrally approved in the EU based on Article 10(3) of Directive 2001/83/EC, i.e. as a hybrid application. [58] The hybrid application was necessary since this product is a concentrate for solution for infusion, i.e. it is a different pharmaceutical dosage form than the lyophilized powder. This makes a generic application impossible. The product contains the active substance as diacid monohydrate which is described as being practically insoluble in water. The crystalline form is described as polymorph B. [58] In a recent publication, two polymorphs of the diacid have been described. [65] In order to overcome the water insolubility, the active substance is formulated with base compounds (diethanolamine, trometamol and meglumine). It was shown by the applicant (Actavis Group) that in aqueous solution, a 1:2 tromethamine salt complex is formed, which appears to be water soluble. Furthermore, L-cysteine and trisodium citrate are added as antioxidants and stabilizer, respectively. [58]

The applicant performed physicochemical and nonclinical studies to compare the new product with the originator Alimta® and to demonstrate equivalence between the two products. Specifically, in two *in-vitro* studies the products were compared over a relevant range of concentrations with respect to their transmembrane transport efficiency. No

apparent differences in the observed transport parameters were observed. However, it was also stated that it is not known which differences in transport parameters would result in clinically significant differences. Therefore, the *in vitro* studies are considered supportive for demonstration of equivalence. [58]

The stability of this drug substance appears to be more critical than that of the disodium salt hydrates, since -20°C was selected as long-term storage condition. Dilution of this concentrate is to be done only with 5% glucose due to a relevant usage patent which must not be infringed. [58, 66] In Section 6.2 of the SmPC it is stated that this product must not be mixed with other medicinal products, specifically cisplatin, since trometamol contained in Armisarte® results in degradation of cisplatin. [66] These specific handling instructions are critical, since they require that the user is fully aware that Armisarte® is not “just another” generic product but differs significantly from the originator. If these handling instructions are not followed, the quality and/or efficacy of the treatment could be impaired. For example, cisplatin, which is part of the combination therapy of NSCLC patients, might be degraded. While the instruction to dilute the product with glucose only can be found on the outer package labelling [66], no specific instruction on the incompatibility with cisplatin is found there, but only in the SmPC. It would have been useful to include these handling instructions on the outer packaging as well.

Even though Armisarte® was approved based on a hybrid application, no new clinical studies such as a BE study have been submitted. This is justified since both the original and the new product are applied intravenously, and independently of the salt form 100% bioavailability is assumed.

In summary, it appears that Armisarte® was primarily developed to circumvent patents covering both the original medicinal product and generic products. While the generic pemetrexed products are handled identical to the original product (storage at ambient conditions, dilution with NaCl), this is not the case for Armisarte®. Here, storage of the drug product is at 2-8°C. These handling differences are summarized in Table 4. The outer package labelling of Armisarte® does not adequately alert the user on these differences.

Table 4: Comparison of Storage and Handling of Pemetrexed Products

	Drug substance	Drug product	
	Retest Period, Storage Conditions	**Shelf life Storage condition (EPAR)**	**Recommended in-use storage (PIL)**
Alimta® 100 mg PFI[3]	Disodium heptahydrate 3 years (no special storage required)	3 years (no special storage required)	24 h (refrigerated temperature)
Pemetrexed Lilly 100 / 500 mg PFI			
Pemetrexed Sandoz 100 mg PFI	Disodium hemipentahydrate 3 years (2-8°C)	2 years (no special storage required)	24 h (2-8°C) "do not use if you notice particles or discoloration"
Ciambra® 100 /500 mg PFI	Disodium hemipentahydrate 2 years (<30°C, inert atmosphere)	2 years (no special storage required)	24 h (refrigerated or 25°C)
Pemetrexed medac 100 / 500 / 1000 mg PFI	Disodium hemipentahydrate 3 years (2-8°C, inert atmosphere)	3 years (no special storage required)	24 h (2-8°C)
Pemetrexed Accord 100 / 500 / 1000 mg PFI	Disodium hemipentahydrate 2 years (2-8°C, inert atmosphere)	3 years (no special storage required)	24 h (2-8°C) "do not use this medicine if you notice any visible signs of deterioration."
Pemetrexed Hospira 100 / 500 / 1000 mg PFI	Disodium hemipentahydrate 2 years(-20°C) 1 year (2-8°C)	3 years (no special storage required)	24 h (2-8°C) "If particulate matter is observed, do not administer"
Armisarte® 4 / 20 / 40 ml concentrate for 100 / 500 / 1000 mg	Diacid monohydrate 12 months (-20°C)	18 months Store and transport refrigerated Protect from light	24 h at 2-8°C "… should not be used if there are any signs of particles"

4.3.2. United States of America

According to the Orange Book, [7] the patent exclusivity period for pemetrexed has expired in November 2015. According to the FDA Website, at the time of thesis writing two ANDAs for pemetrexed disodium have been tentatively approved, but no approval details are available yet. [67]

[3] PFI = powder for concentrate for solution for infusion

4.4. Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug indicated for treatment of pain and inflammation which acts by inhibiting both cyclooxygenase-1 (COX-1) and COX-2 enzymes. Products with diclofenac have been on the market since 1973. [68] In Europe, the original as well as generic and hybrid applications for marketing approval have been submitted in national procedures and/or MRPs and DCPs. Both in Europe and in the USA, many diclofenac products have been authorized for several decades, prior to establishment of the MA procedures outlined in Section 3 of this thesis. Therefore, the discussion in this Chapter focuses on more recently approved diclofenac products for which PARs are available.

The rate of diclofenac absorption after oral administration depends primarily on the salt form. It has been shown to be relatively slow for the sodium salt, while it is faster for the potassium salt, since the latter is more water soluble. [68] Consequently, the sodium salt is used in extended-release products, for example as enteric-coated tablet. Diclofenac potassium is contained in products intended for immediate release, typically in the treatment of acute pain such as migraine. The diclofenac acid is practically insoluble in water [69] but it has been used in one product in the form of nano-sized drug particles with the objective to avoid precipitation of a salt in acidic pH in the stomach. [68] Finally, there are topical products available containing the sodium, epolamine (2-pyrridin-1-ylethanol) or diethylamine salt of diclofenac. The epolamine salt exhibits detergent-like properties leading to an enhanced epidermal penetration. [70] These products have been developed to reduce systemic exposure and to avoid cardiovascular and gastrointestinal side effects of the substance. Thus, diclofenac is an excellent example to illustrate how different salts combined with pharmaceutical technology can lead to a wide variety of medicinal products with different characteristics. An overview of the different salts and pharmaceutical dosage forms is provided in Figure 3.

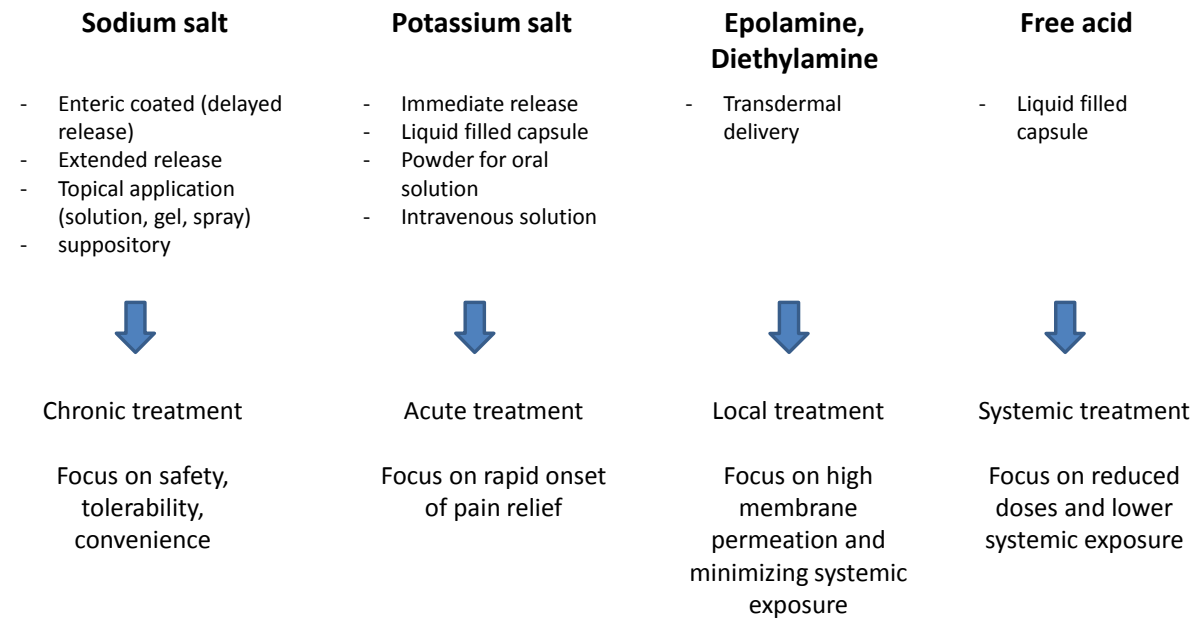

Figure 3: Overview of Most Important Diclofenac Dosage Forms

4.4.1. European Union

For the analysis of diclofenac medicinal products in Europe, the website of Heads of Medicines Agency (HMA) was searched in the Advanced Search modus with the key word "diclofenac" in the category "Active Substance (free text)". [71] This search yielded 67 entries with a medicinal product containing diclofenac. Of these, 36 entries provided a link to a PAR where details on BE testing and on the type of approval can be found. Furthermore, the website of the German Ministry of Health (Bundesministerium für Gesundheit, "Arzneimittelinformation für alle", [72]) was searched with the key word "diclofenac" in the category "Stoffname". This search yielded 210 entries; when the search was limited to entries with a PAR, 7 entries remained. Of those, only four were publicly available. [72] Most PARs analyzed for diclofenac products in Europe are generic products of an original product containing the identical salt and dosage form; however, in most cases the PAR for the original product is not available. Therefore, it was difficult to systematically address the question how the different diclofenac salt and dosage forms were approved initially.

There are also approvals according to Article 10(3), characterized by a novel dosage form and/or a different salt. At least one product was approved according to Article 8 of the Directive 2001/83/EU (Voltarol® 12.5 mg liquid filled capsule). Approvals according to Article 10a (well-established use) can also be found. Contrary to other examples in this thesis, there are no cases where a generic or hybrid application used a different salt as a reference

medicinal product. This illustrates that for diclofenac, the salt properties are significantly different.

In Europe, the branding situation around diclofenac medicinal products is confusing: even though the absorption of diclofenac potassium is significantly faster than that of diclofenac sodium, both salts and topical applications are available under the brand name “Voltaren”, however with an addendum such as “retard”, “rapid”, “T”, “K” or “dispers”.

4.4.2. United States of America

For products in the USA, the FDA website was searched for diclofenac products. [73] All diclofenac products formulated in a novel dosage form were approved as NDA (either as full NDA or as a 505(b)(2) NDA). The branding situation of diclofenac is clearer than in Europe and the brand “Voltaren” is used only for sodium diclofenac.

4.4.3. Overview of Diclofenac Products

In Table 5 through Table 7 an overview of the different diclofenac products is provided. There were significantly more public assessment reports on the FDA homepage available than on the HMA website or on the German information system on medicinal products (Arzneimittelinformationssystem), respectively. Therefore, relevant characteristics such as PK parameter are provided from the US source; it is assumed that these characteristics are similar for the European product.

In addition, in Europe products containing the diethylamine, epolamine and colestyramine salt are available; different dosage forms such as a suppository as sodium salt can also be found. These are summarized in Table 8.

Table 5: Overview of Diclofenac Sodium Products

Description / Dosage Form	USA		Europe
	Product Name [74]	**Comments**	**Exemplary Product***
Delayed release tablet (enteric coated)	e.g. Voltaren®	Treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, ankyloses spondylitis; T_{max}: 2.3 h, absolute BA 55% [75] first approved diclofenac product in USA (NDA, 5 years data exclusivity)	e.g. Voltaren®, Voltarol®, Voltaren® enteric coated tablet [87]
Extended release tablet	e.g. Voltaren-XR®	Treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis T_{max}: 5.3 h, absolute BA 55% [76]	Voltaren® retard [87]
Solution/drops 0.1%	e.g. Voltaren ophthalmic®	Treatment of postoperative eye inflammation, relief of pain and photophobia Systemic plasma levels below limit of quantification of 10 ng/ml [77] No information on type of application and/or new data exclusivity	e.g. Voltaren® 1mg/ml eye drops (hybrid application)
Combination product	e.g. ARTHROTEC®	Enteric coated core with diclofenac, outer sphere with misoprostol (gastroprotective); PK of the individual components similar to PK of individual drugs; Treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis in patients at risk for gastric or duodenal ulcers; T_{max}: 2 – 2.4 h, absolute BA 55% (diclofenac) [78] NDA of combination product, 3 years exclusivity [79]	e.g. Arthrotec® 50 tablets [88]
Topical gel	Voltaren gel® 1%	Treatment of pain of osteoarthritis of joints amenable to topical treatment Systemic exposure approximately 6% of applied oral dosage form [80] 505(b)(2) application	e.g. Voltaren Emulgel®
	SOLARAZE® 3%	Treatment of actinic keratosis; systemic exposure about 10% of applied dose [81] Full NDA, since new indication (5 years data exclusivity)	e.g. Solarase®
Topical solution, 1.5%	PENNSAID®	Treatment of osteoarthritis of the knee; Systemic exposure not compared to oral dose [82]; 505(b)(2) NDA, 3 years new exclusivity [83]	e.g. Pennsaid®
Injection for intravenous application	Dyloject®	Management of pain alone or in combination with opioid analgesics; $T_{max} \leq 5$ min [84]; 55(b)(2) NDA with 3 years new exclusivity [85] Reference is made to safety data of Cataflam 50 mg even though this is the K salt. [86] However, the intravenous application of the Na salt leads to higher C_{max} and shorter t_{max} than the oral K salt	e.g. Voltarol® ampoules (solution for injection)

*if not noted otherwise, no PAR was available

Table 6: Overview of Diclofenac Potassium Products

Description / Dosage Form	USA		Europe
	Product Name [74]	Comments	Product Name*
IR tablet	e.g. Cataflam®	For treatment of primary dysmenorrhea, pain due to osteoarthritis or rheumatoid arthritis. 55% of orally administered dose is bioavailable, t_{max} is approx. 1 hr (fasted). [89] No information on approval type. [74]	e.g. Voltaren Rapid®
Powder for oral solution	e.g. CAMBIA®	For acute treatment of migraine, t_{max} very fast (10-15 min), 55% bioavailability [94] 505(b)(2) NDA with 3 years new exclusivity [90]	e.g. Eminocs® Art 10(3) [92]
Liquid filled capsule	e.g. ZIPSOR®	For relief of mild to moderate acute pain. Formulation contains diclofenac potassium + solubilizing and dispersing agents. C_{max} higher than that of Cataflam, AUC comparable. Shorter t_{max} (0.6 h) than with IR tablet (1.3 h) [91] 505(b)(2) with 3 years new exclusivity	e.g. Voltarol® 12.5 mg liquid capsule Art 8(3)

Table 7: Other Diclofenac Salts

Description / Dosage Form	USA		Europe
	Product Name [74]	Comments	Product Name*
Topical patch, 1.3%	FLECTOR® (Diclofenac epolamine)	For treatment of acute pain due to minor strains, sprains and contusions [95]. T_{max} is approx. 10-20 hours, systemic exposure is < 1% of single dose of 50 mg Na salt	Voltaren Wirkstoffpflaster®
Immediate release capsule	ZORVOLEX® Diclofenac free acid	For management of mild to moderate acure pain and osteoarthritis pain. No BE with diclofenac K tablets (especially with respect to C_{max}). However, t_{max} and AUC comparable to Cataflam. [93] Submicron particles (200 to 800 nm) of free acid are formulated to achieve comparable systemic exposure at lower dosage, preventing precipitation of a salt in the acidic stomach. [68]	Voltaren dispers® [93]

Table 8: Diclofenac Salts Approved only in Europe

Description / Dosage Form	Product Name	Salt Form	Comments
Topical patch	Voltaren® Schmerzpflaster [96]	Na salt	For short-term treatment of local, acute strain or contusion in adults and adolescents > 16 year. [96]
Suppository	Voltaren® Zäpfchen [97]	Na salt	For treatment of acute and chronic arthritis, spondylitis ankylosis. In addition, the 25 mg suppository is approved for treatment of pain in children and adolescents, e.g. in the head-and-neck area. [97]
Topical gel	Voltaren® Emulgel	Diethylamine salt	For treatment of acute strain, contusion. In addition, for short-term treatment of adolescents above 14 years. [98]
Capsule	Voltaren® Resinat [99]	Colestyramin salt	For treatment of acute and chronic arthritis, spondylitis ankyloses. T_{max} around 1.25 hours, c_{max} about 1/3 of equivalent Voltaren® dose

4.5. Perindopril

Perindopril has been developed by Servier as an anti-hypertensive drug acting on the angiotensin-converting enzyme (ACE). The initial approval in 1988 was in France as t-butylamine (erbumine) salt (Coversyl®). In 2005, Servier applied for MA for the arginine salt which is bioequivalent to the erbumine salt but more stable. [100]

At first sight, perindopril appears as an example where an alternative salt was developed in order to improve the initial medicinal product. However, in 2014 an antitrust procedure was published by the European Commission against Servier and several generic companies. [101] In the publicly available part of this procedure, it is described how Servier tried to delay the onset of generic products with a strategy covering several aspects: (i) a multitude of new patents (so-called “blocking or paper patents”) protecting the process and crystalline forms of the drug substance, some of them containing “zero inventive activity” [101] (ii) (unlawful) agreements with generic companies not to enter the market (so-called “reverse payment settlements”), (iii) buying of relevant IP from API manufacturers (that might have allowed circumvention of key patents) or buying the API manufacturer themselves (this violates EU competition law) and (iv) salt change to arginine (patent protection up to 2023) with the unethical strategy to withdraw the erbumine salt as not to allow generic companies to perform BE studies.

Even though Servier was successful in postponing generic competition for up to 4 years until 2007, they were not successful in withdrawing the erbumine salt from the market and preventing BE studies. From a regulatory point of view, this “Servier-exclusive” salt change would have been difficult since in 2003, the erbumine salt had been on the market already for 15 years; theoretically, this might have allowed an application for marketing approval according to Article 10a (well-established use). According to NTA, for such an application “… evidence must be supplied to demonstrate that a constituent has been extensively used for the 10-year period…”. [12] Since perindopril is considered a “blockbuster” drug with wide use in Europe and in the USA, it can be assumed that there would have been sufficient scientific literature available in the public domain, allowing a comparison of a new generic product on this basis instead of a formal BE study. In addition, the MAH needs to announce withdrawal of a product [12] which would have alerted generics companies intending to perform BE studies. Today, both the erbumine salt and the arginine salt are on the market, and in addition a tosylate salt was approved in 2012.

In the USA, there is only generic erbumine salt on the market. Since a salt change is not possible in the frame of an ANDA, the regulatory environment in the USA would not have supported Servier’s strategy to switch from the erbumine to the arginine salt with low efforts.

5. Discussion

Different salts of an active substance can cause a change in the pharmacokinetic and/or pharmacodynamic behavior; this has been illustrated with the examples in Section 4. These differences can be negligible (as likely the case for amlodipine, clopidogrel, pemetrexed, perindopril) or significant and intended (e.g., diclofenac). In this discussion section, an evaluation is made whether the regulatory pathways described in Section 3 are appropriate and whether changes are recommended. In Table 9, the substances of Section 4 are summarized.

Table 9: Summary of Drug Substances Discussed in the Thesis

Substance	BCS class	Reasons for alternative salt
Amlodipine	Besylate: BCS 1 [29] Maleate: BCS 1 Mesylate: BCS 1	Circumvention of originator's patent
Clopidogrel	Hydrogen sulfate: BCS 2 [38] Other salts: no information	Circumvention of originator's patent
Pemetrexed	n/a (i.v. application)	Circumvention of originator's patent
Diclofenac	Na salt: BCS 2 [102] K salt: BCS 2 [102]	Two different salts with different solubilities and drug release characteristics
Perindopril	3 (erbumine) Arginine, tosylate: no information	Originator's attempt to prevent generic products

5.1. Number and Type of BE Studies for IR Dosage Forms

In general, in the EU a generic application for an immediate release formulation drug product of a different salt can be submitted based on only one BE study in the fasted state. [6] Furthermore, a BCS-based biowaiver can be applied in case both the test and reference product are BCS class 1, even if different salts. [6] Normally, the BE study is to be performed under fasting conditions, since this is considered the most sensitive condition to detect a potential difference between formulations. However, in case the salt of the generic formulation is different from the salt of the original formulation, the dissociation of drugs in salt form will depend on the counter ion and on the gastric and intestinal pH. This pH is known to depend on the fed/fasted state. Depending on the dissociation, the drug absorption and consequently the BA may be different in the case of two different salts.

In the USA, even for a generic application where in the ANDA the same salt has to be used as in the NDA, BE is recommended to be demonstrated with two separate studies, one each in the fasted and fed state. Exemptions to this are (i) immediate release formulations where

labelling requires that the drug is to be taken in the fasted state (no fed-state BE study required), (ii) when it was demonstrated that there is no food effect on absorption (no fed-state BE study) or (iii) for BCS I compounds (no in-vivo study required). [103, 104] If a different salt is developed, a 505(b)(2) application is necessary which will require additional clinical data, e.g. PK and/or efficacy studies. Thus, a salt change in the USA is accompanied by a broader clinical data basis than in the EU.

Recommendation: If a generic IR formulation containing an alternative salt is to be developed, for BCS II and IV compounds an additional mandatory fed-state BE study is recommended. Also, for BCS I and III compounds, differences in dissolution profiles at pH 1 and 4.5 would suggest that drug release is influenced by food which should be discussed by the applicant and made publicly available in the PAR. In such cases, a fed state BE study might be recommended. Unclear cases should be discussed with the CA; this might lead to the generation of a product-specific BE Guidance. [105]

Application of recommendation to the examples: All amlodipine salts belong to BCS class 1, and formally a BCS-based biowaiver could have been applied in the EU. This was not done and it suggests that the generic pharmaceutical companies have been aware of the special situation associated with a salt change and decided to present clinical BE data.

Clopidogrel hydrogen sulfate belongs to BCS class 2, there is no information on the other salts. In addition, the salts are prodrugs. The pharmacologically active thiol metabolite is generated in the intestine and liver. Here, the solubility and membrane permeability of the prodrug as well as the intestinal permeability of the thiol metabolite are relevant for the BA of the biologically active molecule. However, to date it is not possible to quantify the biologically active molecule, and only surrogate data on BE and BA are available. In this special case (and independent of the counter ion) it is questionable whether BE data on a surrogate parameter in the *fed state* would contribute relevant information. In this case, it might be more appropriate to monitor alternative salts of clopidogrel with a post-authorization study (see below).

For diclofenac, the various salts are so different that they have been approved as hybrid (EU) or 505(b)(2) (USA), respectively. This implies that more than a BE study was performed.

Perindopril is a BCS class III compound; it is not expected that food will have an effect on drug absorption, therefore performing only one BE study in the fasted state is justified. The recommendation of a second BE study is not applicable to pemetrexed since this drug substance is applied intravenously.

5.2. Requirements for Publicly Accessible Data

In the case that an already known active substance is formulated as an alternative salt in a medicinal product, the medical community knows already the original product. In the EU there may not be awareness of the fact that a different salt is used in the new product which may have been approved as a generic or hybrid application, respectively.

This differentiation is much easier in the USA, since here an ANDA implies that the generic product is as identical to the originator as possible. A medicinal product containing a different salt and approved as a 505(b)(2) is also an NDA and thus it is clearly signaled that the product contains new features.

For a generic medicinal product, a BE study is proof that the generic and original product are therapeutically equivalent. For a medicinal product containing a different salt and being approved as a hybrid application, there will be clinical data on pharmacokinetics, on differences in systemic exposure, on efficacy in a different indication etc. This data should always be publicly available, especially in cases where the medical professional might assume more similarity and interchangeability between two products than actually present. Such information is contained in the PAR, which is accessible on the EMA website for all medicinal products approved in the centralized procedure. However, for medicinal products which underwent a DCP or a MRP, the publication depends on the national CA of the RMS, and most PARs are not available to the public. For example, it was not possible to obtain the PAR on the approval of amlodipine maleate in Sweden from the Swedish CA, or on the approval of the clopidogrel base from the German BfArM. Furthermore, some CAs do not issue a PAR.

There may be cases where a medical professional needs to understand how BE between two different salts was established, or whether in the EU a medicinal product containing a new salt was approved as a generic or as a hybrid product. This information is not found in the SmPC and/or product labelling. The medical professional may want to have affirmation that changes in the salt do not translate into pharmacological changes. He/she has to decide whether it is advisable to stay with the original medicinal product or whether substitution is possible. It must be possible to correlate clinical observations such as in the example of clopidogrel base [49] with data which led to the approval of the medicinal product containing the drug substance. If the ÖKG recommends to the medical community in the case of clopidogrel to stay with the original medicinal product and not to switch to a generic product, either the ÖKG has not been informed sufficiently on the therapeutic equivalence of generic product(s), or this scientific society has sound reasons to recommend the original product instead of a generic alternative.

Furthermore, national agencies responsible for assessment of health technology (e.g., GBA in Germany, NICE in UK) and/or health insurance agencies will recommend switches from the original medicinal product to a less costly alternative as soon as possible; often, insurance agencies generate pricing agreements with generic product companies to preferably reimburse specific generic products. If such products are based on a different salt and have been approved in a hybrid application, the reimbursing company must be fully aware of potential differences.

Recommendation: It is recommended that in case a different salt is approved, publication of the PAR should be mandatory, also in national approvals.

Application to the examples in this thesis: In the case of amlodipine, concerns have been raised in the literature on the exchangeability of the besylate with maleate salt. [4] The concerns are not very specific; the author criticizes primarily the design of BE studies and the missing of pharmacodynamics endpoints. It is difficult to eliminate these concerns, since no public data on the regulatory assessment of the maleate salt are available. Similarly, in the case of clopidogrel base it is not possible to discuss the concerns and clinical observations made by a hospital in Italy. [49]

5.3. Labelling

If a generic medicinal product containing an alternative salt differs from the original medicinal product with respect to shelf life, storage conditions, packaging, handling and/or appearance, patients or health care professionals might be insecure or they might apply handling instructions from the well-known original medicinal product to the generic, new product. One such example is pemetrexed: while the original medicinal product Alimta® (and its generic products) are lyophilisates that do not require any special storage conditions, the hybrid product Armisarte® (solution concentrate) needs to be stored and transported at 2-8°C and protected from light. This deviation from the other pemetrexed products is only found in the SmPC and PIL, but not on the outer carton.

Recommendation: It is recommended that handling and storage conditions differing from the established use of the original product should be placed on the outer packaging and marked in bold font. In case a product was approved under Article 10(3) of Directive 2001/83/EC, there should also be a clear information on the package, labelling and SmPC.

5.4. Post-Authorization Studies

In the examples evaluated in this thesis, there were no cases where a post-approval safety or efficacy study, respectively, has been performed. Briefly, a post-authorization safety study (PASS) aims to identify or characterize a safety hazard, [11] typically in a larger patient population than during the clinical study. A post-authorization efficacy study (PAES) is requested by a CA in order to complement available efficacy data or to eliminate scientific uncertainties; such study can be requested with granting the MA, or after granting the MA when real-life conditions indicate that previous efficacy evaluation may have to be revised. [106]

In the case of clopidogrel base a statistically significant reduction of efficacy was observed. [49] In the EMA Guideline on PAES it is stated that a PAES might be needed "… where there is a well-reasoned scientific uncertainty the resolution of which is important for understanding therapeutic efficacy and benefit risk…". [107] Based on a BE study between the original clopidogrel hydrogensulfate and the base, such difference was unexpected, but in line with the above cited guidance only a PAES could elucidate the concerns. Similarly, it is stated in the EPAR of the recently approved Armisarte® that there is no sound knowledge which *in vitro* differences in membrane transport diffusion of different salt forms can result in clinically significant differences. This could only be elucidated by a PAES.

Recommendation: The CAs should consider more frequently the option of a PAES or PASS, respectively. Due to a salt change very specific situations can arise (such as in the case of clopidogrel) which are difficult to be covered by guidelines.

5.5. Development Rationale and Consequences

The circumvention of a patent is a major driving force for developing a different salt. If a patent protects only the original salt, another salt might be approved prior to that patent expiry, as it was the case with clopidogrel. Here, it is interesting that some of the clopidogrel salts, e.g. HCl, have been approved only for one indication of the originator and not for the other. Most likely, this is also due to patent reasons. Similarly, in the example of pemetrexed, the different handling of Armisarte® is due to patent reasons. In practice one cannot expect that the user will be aware of these limitations. If the physician prescribes a generic or hybrid medicinal product, he/she may not be alerted to the fact that the indication is limited and/or that the handling should be different.

Recommendation: In cases where limitations in freedom to operate lead to the development of a hybrid product with different application instructions and/or changes in the medical

indications, it is recommended that the CA requires the applicant to investigate whether the accidental use/application of the hybrid product as the original medicinal product bears a risk to the patient. For example, in the case of Armisarte® it should be tested by the applicant whether the accidental dilution of the concentrate with NaCl instead of glucose leads to an impairment of the product.

5.6. Branding

In the case of different oral dosage forms of diclofenac in Europe, branding is misleading since all products are called "Voltaren®", irrespective of their pharmacokinetic behavior. If Voltaren® is the brand for the slow release formulation, a new IR formulation (such as the potassium salt) should not be called Voltaren®, even if an addendum such as "rapid" is provided. This has been solved better in the USA, where Voltaren® is used only for products containing the Na salt, and products with the K salt have different names.

Recommendation: In the case of alternative salts, branding of different products should not be misleading, so that the pharmacists, physician and patient can correlate the brand with a specific property of the medicinal product.

5.7. Multiple Pre-clinical Studies

If there are differences in properties of a new, alternative salt, prior to its approval as generic medicinal product additional preclinical studies might be required as outlined in [11]. In the examples investigated, this was the case for the clopidogrel HCl salt, amlodipine maleate and mesylate salt.

In the case of clopidogrel HCl salt, EPARs are available on several products by different generics companies, which were all approved with the centralized procedure. Of these, five are still authorized at the time of accessing the data base. All applicants submitted preclinical data, i.e. a single dose toxicity study and a 13-week repeated dose toxicity study in rats. The wording of the scientific discussion on non-clinical aspects in these EPARs is identical for the products investigated. This suggests that the development of the HCl salt might have been out licensed from one generics company to others. However, it might also be that the compound was repeatedly evaluated in more or less identical preclinical studies. In addition, there are several products approved in MRP or DCP procedures, respectively. [108] For these products PARs are not available, but there is also the potential for duplicate *in vivo* studies.

In the case of amlodipine maleate, no PARs are publicly accessible even though there are many generic products based on this salt. In the referral [22] regarding the first product with maleate it is stated that preclinical studies were submitted to qualify impurities inherent to the maleate salt. For amlodipine mesylate, one PAR is available describing a single dose toxicity study and a repeated dose toxicity study in rats. It is assumed that the other applicants performed similar preclinical studies.

These preclinical studies are to be performed by the generics applicant who will otherwise refer to clinical and preclinical data of the originator. If there are several generics applicants and the nature of the alternative salt requires additional preclinical studies, there is a risk that each generics company performs its own preclinical study, since there is no legal basis for them to refer to each other's preclinical data. Furthermore, it depends on the applicant's line of argumentation and physicochemical data of the alternative salt to determine whether additional preclinical data are required.

Recommendation: It is recommended that for ethical reasons, generics companies submitting a MAA for a medicinal product containing an alternative salt should be able to refer to preclinical data on that salt of another applicant. These preclinical data are typically needed to demonstrate equivalent pharmacodynamics or toxicological behavior in animals, and it is not expected that they will be different from one company to another. These preclinical data are not indended to demonstrate BE between different (proprietory) formulations. The latter must always be addressed by a human BE study.

6. Conclusion and Outlook

Even though the development of alternative salts as generic or hybrid applications is often driven by cost pressure on the generics company (due to price competition and due to the saving efforts of the national health insurance systems), it is the task of regulatory authorities to weigh the benefit-risk ratio of new medicinal products and to decide whether an alternative salt can be approved in a similar fashion as a generic medicinal product, or whether additional information is needed to demonstrate comparable safety and efficacy. This should be decided on a case-by case basis, and special emphasis should be on demonstration of BE, on availability of public PARs, clear labelling and branding, post-authorization studies and the avoidance of duplicate preclinical studies.

7. Summary

In Table 10 the regulatory pathways for a different salt in the EU and USA, respectively, are summarized. The most important difference between EU and USA is that in the USA,

approval of a different salt as a purely generic medicinal product is not possible. In the EU, a different salt can be approved as generics, provided the requirements outlined in Section 3.1 are fulfilled. Thus, in the USA a stricter regulatory pathway is prescribed, the pathway in the EU provides more flexibility.

Table 10: Regulatory Pathways for a Pharmaceutical Alternative in EU and USA

	Regulatory Pathway	
	EU	**USA**
Generics application	Possible	Not possible
"Hybrid" application (Article 10(3) of Dir. 2001/83/EC in EU, 505(b)(2) in USA)	Possible	
Full dossier	Possible	

Furthermore, the hybrid application according to Article 10(3), Directive 2001/83/EC and the NDA according to Section 505(b)(2) of the FD&C Act differ from each other as described in Table 11.

Table 11: Characteristics of the Hybrid Application and the 505(b)(2) NDA

	EU: hybrid	**USA 505(b)(2)**
When?	New dosage form, strength, route of admin, indication, change to substance	
Required for different salt?	Only if different properties with respect to safety and/or efficacy	yes
What to submit?	No full dossier. Applicant relies in part on innovator's data, provides some data himself	
Market exclusivity?	No	0-5 years
New IP?	Possible	

Based on the data and examples presented it is concluded that even though the regulatory pathway in the EU is more flexible, it needs optimizations as outlined in Section 5 to ensure safety and efficacy of medicinal products based on a different salt. The most effective way would be an amendment of Directive 2001/83EC such that a different salt cannot be approved any longer according to Article 10(1) of Directive 2001/83, but must follow Article 10(3) instead. This change should be accompanied by guidelines and/or adaptations of existing guidelines, addressing the issues raised in Section 5 of this thesis.

9. References

[1] Stahl, P.H., Wermuth, C.G. (2008) (ed) Handbook of Pharmaceutical Salts. Properties, Selection and Use. Zürich, Switzerland Verlag Helvetica Chimica Acta

[2] Patel, A., Jones, S.A., Ferro, A., Patel, N. (2009): Pharmaceutical salts: a Formulation Trick or a Clinical Conundrum? Br. J. Cardiol. 16: 281-286.

[3] Verbeeck, R.K., Kanfer, I., Walker, R.B. (2006): Generic Substitution: The Use of Medicinal Products Containing Different Salts and Implications for Safety and Efficacy. Eur. J. Pharm. Sciences 28: 1-6.

[4] Meredith, P. (2009): Potential Concerns about Generic Substitution: Bioequivalence versus Therapeutic Equivalence of Different Amlodipine Salts. Curr. Med. Res. Opin. 25: 2179-2189.

[5] Kukin, M.L., Mannino, M.M., Freudenberger, R.S., Kalman, J., Buchholz-Varley, C., Ocampo, O. J. (2000): Hemodynamic Comparison of Twice Daily Metoprolol Tartrate with Once Daily Metoprolol Succinate in Congestive Heart Failure. Am. College Cardiology 35: 45-50.

[6] EMA (2010): CPMP/EWP/QWP/1401/98 Rev.1, Guideline on the Investigation of Bioequivalence. URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf, accessed 08/04/2016

[7] US Department of Health and Human Services: Approved Drug Products with Therapeutic Equivalence Evaluations, 36th edition, Orange Book. 2016

[8] US FDA, Code of Federal Regulations (CFR), Title 21, Part 320, Section 320.1. URL http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.1, accessed 09/04/2016.

[9] EMA/CPMP/EWP/280/96 Corr1: Guideline on the Pharmacokinetics and Clinical Evaluation of Modified Release Dosage Forms. URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177884.pdf, accessed 09/04/2016

[10] EMA/CHMP/281825/2015: Guideline on Clinical Development of Fixed Combination Medicinal Products. URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/05/WC500186840.pdf, accessed 09/04/2016

[11] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use. (as amended) URL http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf, accessed 09/04/2016

[12] European Commission, Health and Food Safety Directorate-General: Notice to Applicants, Volume 2A: Procedures for Marketing Authorisation, Chapter 1: Marketing Authorisation. European Commission, July 2015. URL http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm, accessed 09/04/2016

[13] Federal Food, Drug and Cosmetics Act (FD&C Act), Section 505(b)(2)

[14] US FDA Guidance for Industry: Applications Covered by Section 505(b)(2), Draft Guidance, FDA, 1999, URL http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf, accessed 09 May 2016

[15] MHRA: PAR on Voltarol 12.5 mg Liquid Capsules (Diclofenac Potassium), URL http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con454370.pdf, accessed 26/05/2016

[16] IFPMA (International Federation of Pharmaceutical Manufacturers and Associations): Data Exclusivity: Encouraging Development of New Medicines, 2011, URL http://www.ifpma.org/wp-content/uploads/2016/01/IFPMA_2011_Data_Exclusivity__En_Web.pdf, accessed 11 June 2016

[17] Kumar, M., Jethwani H. (2010): The 505(b)(2) Drug Development Pathway: When and how to Take Advantage of a Unique American Regulatory Pathway. URL www.raps.org/WorkArea/DownloadAsset.aspx?id=3647, accessed 29/07/2016

[18] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphans. URL http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF, accessed 09/04/2016

[19] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on Medicinal Products for Paediatric Use. URL http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf, accessed 09/04/2016

[20] EMA Assessment Report Pursuant to Article 30 of Directive 2001/83/EC: Norvasc and Associated Names. URL

http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Norvasc_30/WC500124849.pdf, accessed 07/08/2016

[21] Heads of Medicines Agencies: MRI Product Index. URL http://mri.medagencies.org/Human/. Advanced search with search term “Amlodipine” and “Amlodipine Besylate”, accessed 13/03/2016

[22] CPMP: Opinion Following an Article 29 Referral for Talam, INN: Amlodipine. EMEA/CPMP/540/04. URL http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Talam_29/WC500010734.pdf, accessed 03/04/2016

[23] Heads of Medicines Agencies: MRI Product Index. URL http://mri.medagencies.org/Human/. Advanced search with search term “Amlodipine”, “Amlodipine Maleat” and “Amlodipine Maleate”, accessed 03/04/2016

[24] Bundesministerium für Gesundheit: Arzneimittel-Informationssystem, URL https://www.pharmnet-bund.de/static/de/index.html, *Recherche für Fachkreise*, Search with search term “Amlodipine”, “Amlodipine Maleat” and “Amlodipine Maleate”. Accessed 03/04/2016

[25] Heads of Medicines Agencies: MRI Product Index. URL http://mri.medagencies.org/Human/. Advanced search with search term “Amlodipine” and “Amlodipine Mesylate”. Accessed 13/03/2016

[26] Heads of Medicines Agencies: PAR Amloblet (Amlodipin Mesilat). URL http://www.hma.eu/fileadmin/dateien/pipar/dk883amlobet/par_DK883_amlobet_20060220.pdf , accessed 03/04/2016

[27] United States District Court for the Western District of Pennsylvania: Findings of Fact and Conclusions of Law, Pfizer Inc. versus Mylan Laboratories, 2007, URL http://www.orangebookblog.com/files/pfizer_v.%20Mylan%20FFCL.pdf, accessed 09 July 2016

[28] European Pharmacopeia, EDQM, 8th edition

[29] Olusola, A.M., Olubukola, O.O., Emeka, O.H., Lilian, A.E. (2012): Two Generic Brands of Amlodipine Besylate under Biowaiver Conditions. Int. J. Pharm. Pharm. Sci. **4**: 265-268

[30] Medicines Evaluation Board in the Netherlands. PAR Amlober. URL http://db.cbg-meb.nl/mri/par/nlh-0814-001-002.pdf, accessed 07/08/2016

[31] MHRA, PAR for Amlodipine Besylate Orodispersable Tablet, URL http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con241806.pdf, accessed 11 June 2016

[32] Mignini, F., Tomassoni, D., Traini, E., Amenta, F. (2007): Single-dose, Randomized, Crossover Bioequivalence Study of Amlodipine Maleate Versus Amlodipine Besylate in Healthy Volunteers. Clin. Exp. Hypertens., 29: 539-52.

[33] Pfizer Inc. Amlodipine Citizen Petition to FDA, Oct 11, 2002. URL http://www.fda.gov/ohrms/dockets/dockets/07p0111/07p-0111-psa0001-02-Tab-01-Pfizer's-Petition-vol1.pdf, accessed 03/04/2016

[34] US District Court Ruling, Case No. 03-02346 Pfizer Inc. v. FDA, Defendants, and Dr. Reddy's Laboratories, proposed Intervenor-Defendants. URL http://www.fda.gov/ohrms/dockets/dockets/06p0077/06p-0077-cp00001-05-Tab-D-vol1.pdf, accessed 03/04/2016

[35] FDA, Center for Drug Evaluation and Research. Application Number 22-026, Summary Review. URL http://www.fda.gov/ohrms/dockets/dockets/06p0077/06p-0077-cp00001-05-Tab-D-vol1.pdf, accessed 03/04/2016

[36] Plavix: EPAR – Procedural Steps Taken Before Authorization. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000174/WC500042186.pdf, accessed 03/04/2016

[37] Plavix Summary of Product Information. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000174/WC500042189.pdf, accessed 10/04/2016

[38] Lassoued, M.A., Khemiss, F., Sfar, S. J. (2011): Comparative Study of Two *In Vitro* Methods for Assessing Drug Absorption: Sartorious SM 16750 Apparatus *Versus* Everted Gut Sac. Pharm. Sci. 14: 117-127

[39] Pereillo, J.-M., Maftouh, M., Andrieu, A., Uzabiaga, M.-F., Fedeli, O., Savi, P., Pascal, M., Herbert, J.-M., Maffrand, J.-P., Picard, C. (2002): Structure and Stereochemistry of the Active Metabolite of Clopidogrel. Drug Metab. Dispos. 30: 1288–1295.

[40] CHMP, Questions & Answers: Positions on Specific Questions Addressed to the Pharmacokinetics Working Group. EMA/618604/2008 Rev. 13. URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002963.pdf, accessed 08/04/2016

[41] Nirogi, R.V.S., Kandikere, V.N., Mudigonda, K. (2006): Effect of Food on Bioavailability of a Single Oral Dose of Clopidogrel in Healthy Male Subjects. Arzneimittelforschung 56: 735-739.

[42] Public Statement on Possible Interaction between Clopidogrel and Proton Pump Inhibitors. EMEA/328956/2009. URL http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/11/WC500014409.pdf, Accessed 29 March 2016

[43] Zupancic, V., Smrkolj, M., Benkic, P., Simonic, I., Plevnik, M., Ritlop, G., Kristl, A., Vrecer, F. (2010): Preformulation Investigation of some Clopidogrel Addition Salts. Acta Chim. Slov. 57**:** 376–385.

[44] Generics Web Industry Newsletter, URL http://www.genericsweb.com/download/DIF%20Clopidogrel.pdf, accessed 30 March 2016

[45] EPAR on Clopidogrel Dura. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001132/WC500028363.pdf, accessed 31/03/2016

[46] EPAR on Clopidogrel Acino. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001166/WC500026971.pdf, accessed 31/03/2016

[47] Tsoumani, M.E., Ntalas, I.V., Goudevenos, J.A., Tselepis, A.D. (2015): Evaluating the Bioequivalence of Clopidogrel Generic Formulations. Curr. Med. Res. Opin. 31: 861-864.

[48] EMA Outcome of a Procedure under Article 29 of Directive 2001/83/EC on Clopidogrel Orion, URL http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Clopidogrel_Orion_29/WC500111635.pdf, accessed 11 July 2016

[49] Marcucci, R., Paniccia, R., Gori, A.M., Gensini, G.F., Abbate, R. J. (2013): Bioequivalence in the Real World is a Complex Challenge. The Case of Clopidogrel. Am. Coll. Cardiology 61: 594-595.

[50] Österreichische Kardiologische Gesellschaft, Stellungnahme zu Clopidogrel. URL http://kardiologie-gefaessmedizin.universimed.com/artikel/stellungnahme-der-%C3%B6sterr-kardiologischen-gesellschaft-%C3%B6kg-zu-clo , accessed 08/04/2016.

[51] Baumgärtel, C. (2012): Generic Clopidogrel – the Medicine's Agency's Perspective. Generics and Biosimilars Initiative Journal 1: 89-91.

[52] EPAR on Clopidogrel Teva. URL (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001053/WC500031168.pdf, accessed 31/03/2016

[53] EPAR on Clopidogrel Teva Pharma B.V. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001226/WC500108104.pdf, accessed 31/03/2016

[54] Kim, S.H., Sung, J.-H., Shin, J., Lee, H.J., Lee, H.S., Cho, D.K., Lim, S.W. (2015): Assessment of the Efficacy and Tolerability of Clopidogrel Napadisilate in Korean Patients with Coronary Stenting: a Multicenter, Prospective, Open-label, Randomized Trial. Curr. Med. Res. Opin. 31: 449–457.

[55] Kovacic, J.C., Mehran, R., Sweeny, J., Li, J.R., Moreno, P., Baber, U., Krishnan, P., Badimon, J.J., Hulot, J.-S., Kini, A., Sharma, S.K. (2014): Clustering of Acute and Subacute stent Thrombosis Related to the Introduction of Generic Clopidogrel. J. Cardiovasc. Pharmacol. Ther. 19: 201-208.

[56] Kondola, S., Manners, D., Nowak, A.K. (2016): Malignant Pleural Mesothelioma: an Update on Diagnosis and Treatment Options. Ther. Adv. Respir. Dis., in press.

[57] Bluthgen, M.V., Besse, B. (2015): Second-line Combination Therapies in Nonsmall Cell Lung Cancer without Known Driver Mutations. Eur. Respir. Rev. 24: 582-593.

[58] EPAR on Armisarte®, previously Pemetrexed Actavis, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004109/WC500200459.pdf, accessed 16/04/2016

[59] EPAR on Alimta. URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000564/WC500025606.pdf, accessed 16/04/2016

[60] European Patent Office, EP1259513, A Novel Crystalline Form of N- 4- 2-(2-Amino-4,7-dihydro-4-oxo-3H-pyrrolo 2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic Acid and Process thereof.

61] EPAR on Pemetrexed Sandoz, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004011/WC500194773.pdf, accessed 16/04/2016

[62] EPAR on Pemetrexed Medac, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004011/WC500194773.pdf, accessed 16/04/2016

[63] EPAR on Pemetrexed Accord, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004072/WC500200626.pdf, accessed 16/04/2016

[64] EPAR on Pemetrexed Hospira, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003970/WC500197786.pdf, accessed 16/04/2016

[65] Michalak, O., Laszcz, M., Jatczak, K., Witkowska, A., Bujak, I., Groman, A., Cybulski, M. (2015) New Polymorphic Forms of Pemetrexed Diacid and Their Use for the Preparation of Pharmaceutically Pure Amorphous and Hemipentahydrate Forms of Pemetrexed Disodium. Molecules 20: 13814-13829.

[66] SmPC of Armisarte®, URL http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004109/WC500200456.pdf, accessed 17/04/2016

[67] FDA Website, URL https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=PEMETREXED, accessed 17/04/2016

[68] Altman, R., Bosch, B., Brune, K., Patrignani, P., Young, C. (2015): Advances in NSAID Development: Evolution of Diclofenac Products Using Pharmaceutical Technology. Drugs 75: 859-877.

[69] FDA Chemistry Review on Zorvolex, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204592Orig1s000ChemR.pdf, accessed 25/04/2016

[70] Rainsford, K.D., Kean, W.F., Ehrlich, G.E. (2008): Review of the Pharmaceutical Properties and Clinical Effects of the Topical NSAID Formulation, Diclofenac Epolamine. Curr. Med. Res. Opin. 24: 2967-2992.

[71] Head of Medicines Agencies, MRI Product Index, URL http://mri.medagencies.org/Human/Product/AdvancedSearch, Advanced search with search term “Diclofenac” in “Active Substance”, accessed 18/04/2016

[72] Bundesministerium für Gesundheit, Arzneimittelinformationssystem, URL https://www.pharmnet-bund.de/static/de/index.html, accessed 25/04/2016

[73] FDA Website for approved drug products, URL https://www.accessdata.fda.gov/scripts/cder/drugsatfda/, accessed 17/04/2016

[74] FDA Website to search for medicinal products, URL https://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm, accessed 23/04/2016

[75] Label (SmPC) on Voltaren Tablet, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019201s039s040lbl.pdf, accessed 24/04/2016

[76] Label (SmPC) on Voltaren XR, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020254s019s020lbl.pdf, accessed 24/04/2016

[77] SmPC on Voltaren Ophthalmic, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020037s031lbl.pdf, accessed 28/06/2016

[78] SmPC on Arthrotec, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020607s031lbl.pdf, accessed 28/06/2016

[79] FDA Administrative and Correspondence Documents on Arthrotec, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20607_ARTHROTEC%20TABLETS_ADMINDOCS.PDF, accessed 24/04/2016

[80] SmPC on Voltaren Gel, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022122s010lbl.pdf, accessed 28/06/2017

[81] SmPC on SOLARAZE Gel, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021005s016lbl.pdf, accessed 28/06/2016

[82] SmPC on Pennsaid, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020947s010s011lbl.pdf, accessed 28/06/2016

[83] FDA Administrative and Correspondence Documents on Pennsaid, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/020947s000admincorres.pdf, accessed 24/04/2016

[84] SmPC of Dyloject, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022396s003lbl.pdf, accessed 28/06/2016

[85] FDA Administrative and Correspondence Documents on Dyloject, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022396Orig1s000Admincorres.pdf , accessed 24/04/2016

[86] FDA Clinical, Pharmacology and Biopharmaceutics Review, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/022396Orig1s000ClinPharmR.pdf , accessed 02/07/2016

[87] Novartis SmPC on Voltaren Enteric Coated and Retard, URL https://portal.dimdi.de/amispb/doc/2014/09/19/2114652/OBFME9F837A801CFCA32.pdf, accessed 26/06/2016

[88] Pfizer Ltd. Arthrotec SmPC, URL https://www.medicines.org.uk/emc/medicine/10673#ORIGINAL, accessed 02/07/2016

[89] Novartis SmPC on Cataflam, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020142s027lbl.pdf, accessed 02/07/2016

[90] FDA Administrative and Correspondence Documents on Cambia, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022165s000Admincorres.pdf, accessed 24/04/2016

[91] FDA Administrative and Correspondence Documents on Zipsor, URL http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022202s000admincorres.pdf, accessed 24/04/2016

[92] PAR on Eminocs (Diclofenac Potassium for Oral Solution), URL http://db.cbg-meb.nl/mri/par/nlh-0800-001.pdf, accessed 02/07/2016

[93] Novartis SmPC on Voltaren Dispers, URL https://portal.dimdi.de/amispb/doc/2014/09/19/0164351/OBFME32E255D01CFCA32.pdf, accessed 02/07/2016

[94] Depomed SmPC on Cambia, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022165s011lbl.pdf, accessed 02/07/2016

[95] Pfizer Inc., Flector SmPC, URL http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021234s013s014lbl.pdf, accessed 02/07/2016

[96] Novartis SmPC on Voltaren Schmerzpflaster, URL https://portal.dimdi.de/websearch/servlet/FlowController/Documents-display#__DEFANCHOR__, accessed 02/07/2016

[97] Novartis SmPC on Voltaren Zäpfchen, URL https://portal.dimdi.de/amispb/doc/2014/09/19/2114653/OBFMEA49479C01CFCA32.pdf, accessed 02/07/2016

[98] Novartis SmPC on Voltaren Emulgel, URL https://portal.dimdi.de/amispb/doc/2015/08/06/2107043/O6a7bf3e423c64118a746291e2d754db3.pdf, accessed 02/07/2016

[99] Novartis SmPC on Voltaren Resinat, URL https://portal.dimdi.de/amispb/doc/2014/09/19/2117982/OBFMEAAD6A6001CFCA32.pdf, accessed 02/07/2016

[100] Telejko, E. (2007): Perindopril Arginine: Benefits of a New Salt of the ACE Inhibitor Perindopril. Curr. Med. Res. Opin. 23: 953-960.

[101] European Commision, Antitrust Procedure Case AT.39612 – Perindopril (Servier), URL http://ec.europa.eu/competition/antitrust/cases/dec_docs/39612/39612_11972_5.pdf, accessed 16 May 2016

[102] Chuasuwan, B., Binjesoh, V., Polli, J.E., Zhang, H., Amidon, G.L., Juninger, H.E., Midha, K.K., Shah, V.P., Stavchansky, S., Dressman, J.B., Barends, D.M. (2009): Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Diclofenac Sodium and Diclofenac Potassium. J. Pharm. Sci. 98: 1206-1219

[103] US FDA Guideline for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies, URL http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf, accessed 01/05/2016

[104] US FDA Guideline for Industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, URL http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf, accessed 01/05/2016

[105] EMA Concept Paper on the Development of Product-Specific Guidance on Demonstration of Bioequivalence, URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/07/WC500147001.pdf, accessed 03/07/2016

[106] Regulation (EC) No 357/2014 of the European Parliament and of the Council of 3 Feb 2014 Supplementing Directive 2001/83/EC, URL http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_357/reg_2014_357_en.pdf, accessed 03/07/2016

[107] EMA Scientific Guidance on Post-Authorisation Efficacy Studies (Draft), 2015, URL http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/11/WC500196379.pdf, accessed 03/07/2016

[108] HMA Website, Product Index, URL http://mri.medagencies.org/Human/Product/AdvancedSearch, accessed June 12, 2016. Search with keyword “Clopidogrel”, dataset further searched for “Hydrochloride”

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

Dr. Brita Schulze