Parallel import of generic medicinal products - Possible impacts of the Kohlpharma Case

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Abbreviations

AUC	Area Under the Curve (of the plasma concentration curve)
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for medicinal products and medical devices, Germany)
Cmax	maximal plasma concentration
EEA	European economic Area
EC	European Community
ECJ	European Court of Justice
EMEA	European Medicines Agency
EU	European Union
MHRA	The Medicines Control Agency, UK
pil	patient information leaflet
UK	United Kingdom
SmPC	Summary of Product Characteristics
tmax	time passed since administration at which the plasma concentration maximum occurs

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1 Introduction

> ***"Over a period of some 25 years, the trade in both generic equivalents and parallel imports has greatly expanded, and their availablity has resulted in considerable cost savings both to the health services and to patients"***
>
> *Drugs and Money, Dukes MNG et al (editors), World Health Organisation Regional Office for Europe, IOS Press, 2003*

All across Europe healthcare costs are rapidly increasing and reforming the health care system has become one of the main objectives in politics. Every possibility to control the healthcare budget, e.g. by lowering the pharmaceutical expenditure, is therefore in the interest of the Community.

In this respect, parallel imported medicinal products and generic medicinal products have the same goal - representing competitively priced therapeutic equivalents to originator pharmaceuticals. Despite of this common goal, parallel imported and generic medicinal products are based upon different principles and consequently are regulated differently, especially with regards to the requirements for a marketing authorisation.

However, when analysing the recent case on parallel imports, that was resolved by the ECJ in Luxembourg in April 2004, Kohlpharma vs. Federal Republic of Germany (C-112/02) [1], the distinction between parallel import licence applications and generic licence applications seems to be blurred. Additionally, the question is raised, whether generic medicinal products can also be imported in parallel instead of having to take the route via a mutual recognition procedure.

In order to assess the possibility of such a scenario and the consequences, this paper first presents an overview of the regulatory framework for both generic and parallel imported medicinal products, especially comparing the situation before and after the Kohlpharma Case.

Furthermore, to gain a realistic picture of the practical consequences of the judgement, the guidelines on parallel importation of the various Member States, if available, are analysed with regards to the new requirements for a parallel import authorisation. Based upon these results, it is finally evaluated whether a generic parallel import application could be successful.

2 Generic medicinal products

Generally speaking, a generic medicinal product is a pharmaceutical product for which the original patent has expired. Any manufacturer may then produce and market it, provided that the new manufacturer obtains the necessary manufacturing and marketing authorisation from the regulatory authorities (see section 2.2) [2]. Hence, generic medicinal products are not completely new products. They contain the same active ingredient (qualitatively and quatitatively) and are essentially similar to the original products (see section 2.1). Consequently, they can be used as equivalents to originator products. The originator´s brand name, however, can not be used. Instead, generic manufacturers mostly market the product under its International Nonproprietary Name (INN) plus the company name. Furthermore, generic medicinal products are sold well below the price of the originator and thereby contribute to lowering the health care cost by substituting the originator product. Therefore, the principle of 'substitution' has been made mandatory for pharmacists and/or physicians in many countries (e.g. in Germany with the so-called 'aut-idem' regulation established in 2002 with paragraph 129 Art. 1.1 SGB V [3]).

2.1 Definitions & Legal Framework

The term "generic" is widely used, but a clear definition was not included in any binding law until April 2004, when the new pharmaceutical legislation, also called 'Review 2004', was adopted by the European Commission.

Prior to the review 2004, the legislation was based upon the concept of "essential similarity" (Article 10 of Directive 2001/83/EC [4]), which was originally delivered by the ECJ in the Generics (UK) Case (Case C 368/96 in which judgement was given on 3 December 1998 [5]).

The new Directive 2004/27/EC amending Directive 2001/83/EC [6] abandoned the concept of 'essential similarity' and instead inserted a clear definition of the term 'generic medicinal product' in the new Article 10 (2) (b):

" 'generic medicinal product' shall mean a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the

reference medicinal product, and whose bioequivalence with the reference product has been demonstrated by appropriate bioavailablity studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be the same active substances unless they differ siginificantly in properties with regard to safety and/or efficacy. (...) The various immediate-release oral pharamceutical forms shall be considered to be one and the same pharmaceutical form. (...)".

However, this definition is not complete without the definition of a 'reference medicinal product', given in Article 10 (2) (a):
" 'Reference medicinal product' shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Aricle 8;"
Hence, the marketing authorisation of the reference medicinal product has to based upon a full documentation including results of pharmaceutical, pre-clinical tests and clinical trials. Article 10 (1) further specifes in the third subparagraph that the critera of a 'reference medicinal product' is still fulfilled even though this product is not authorised in the Member State where the application for a generic product is submitted: "*In this case, the applicant shall indicate in the application form the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is sumbitted, the competent authority of the other Member State shall transmit ... the full composition of the refernce product and if necessary other relevant documentation*."

The regulatory framework is thus mainly formed by the rules provided in Directive 2001/83/EC as amended (and its implementation into national law).

Other relevant areas of law mainly concern the rules relating to Intellectual Property Rights.

Intellectual Property Rights (IPR)
Intellectual Property Rights (IPR) reward and promote innovations. Medicinal products are also covered by IPR, which include for example the data protection period (see section 2.2) and patents respectively Supplementary Protection Certificates (SPC). Patents are available for a medicinal product´s substance, compounds, formulation, usage, process, mechanism of action etc. They are granted on a national basis and are valid up to a period of 20 years.

However, due to fact that the time it takes to otbain a patent and to develop the medicinal product is very long, the period where the patent can actually be used, is much shorter. Hence, a patent is extendable by the SPC to a further maximum period of five years (after the expiry of the original patent term) [7]. Patents and SPCs, however, are not part of the assessment at regulatory authorities, but have to be taken into consideration when wishing to place a product on the market.

2.2 Regulatory framwork for generic medicinal products

As originator products, generics medicinal products have to have obtained a marketing authorisation before they can be placed on the market (see Article 6 of Directive 2001/83/EC). With regards to the documentation that needs to be submitted in order to receive such a marketing authorisation, there are exemptions included in Community law in order to avoid unnessesary duplication of tests on animals or humans. Hence, an applicant for a generic medicinal product is not required to provide results of pre-clinical tests and clinical trials, provided that he can demonstrate that the product is a generic of a 'reference medicinal product' (see Articles 10 (2) (a) and (b) above). Such an application is called an **'abridged' or 'generic' application**. In such an application, the applicant may instead refer to the data on safety and efficacy already established by the originator.

To ensure, that innovative firms are not placed at a disadvantage, the inventor is granted a period of so-called **'data exclusivity'** (see also section 2.1 under 'IPR'). During this period, a generic applicant and the authorites can not rely on to the data filed by the original applicant for a granting a marketing authorisation.

Currently, the data exclusivity period is either six or ten years, depending on the type of marketing authorisation procedure and the Member State where the application is submitted (Article 10 (1a) (iii) of Directive 2001/83/EC, see page 60). '6-year countries' for example are Austria, Denmark, Finland, Greece, Ireland, Portugal, Spain, Norway and Iceland [8]. However, 'full' applications (falling under the definition for a reference product accoridng to Article 10 (2) (a) of Directive 2004/27/EC), which are submitted after October 30, 2005 will be granted a data protection period of 8 years. After this period, a generic manufacturer can

submit an abridged application with the originator as reference medicinal product. Additionally, the data exclusivity period is extended by another 2 years of market exclusivity (which again is extendable by another year if the originator obtains an authorisation for one or more therapeutic indications of significant clincial benefit within the first eigth years after the issue of the first licence). In the end, a market access is not possible for a generic product after 8 + 2 (+1) years after the initial authorisation of the originator product. This new provision, which harmonised the effective data respectively market exclusivity period throughout the EU/EEA to at least 10 years, was included with the new EU Pharmaceutical Legisation adopted in 2004 (Article 10 (1) of Directive 2004/27/EC first and second subparagraph). As the new protection period is valid for applications filed after October 30, 2005 only, this provision will come into effect for generic applications at the earliest in November 2013 (2005 + 8 years + ? years assessment time).

As soon as a marketing authorisation is granted for a generic medicinal product in one Member State, a second marketing authorisation in another Members State can only be granted via the mutual recognition procedure (MRP), see Art. 17 (1) and 28 (2) of Directive 2001/83/EC as amended. The MRP is a 90 day procedure with no clock stops. During the procedure, the marketing authorisation originally granted by the so-called Reference Member State (RMS) should be ‘mutually recognised’ by the other Member States involved (so-called ’Concerned Member States’ or CMS). Upon finalisation or the MRP, the CMS officially have further 30 days to grant national marketing authorisations (for further guidance see Chapter 2 of Volume 2A Notice to Applicants [9]).

Other marketing authorisation procedures, in case no marketing authorisation exists in any Member State, are the decentralised procedure (DCP) or, in case the originator product has been authorised centrally, the centralised procedure (according to Regulation 726/2004/EC [10]. With regars to the parallel importation of generic medicinal products, however, especially the MRP is of relevance.

3 Parallel import of medicinal products - situation before April 1st 2004

Parallel trade (or parallel imports) in general is defined as a *„trade in products which takes place outside the official distribution system set up by a particular firm. Parallel traders buy products in countries where they are sold at lower prices and sell them in high-price countries. The flow of products thereby created is called parallel trade."* [11]. Hence, parallel import is a cross-border trade within the Community through a route that the manufacturer has not originally intended - driven from price differences between the Member States. The reasons for such price differences for pharmaceuticals are two-fold. On the one hand, prices are set by national governments to control the health care expenditure, on the other hand there is active price differentiation policy by the pharmaceutical industry. Currently, only originator products are being traded in parallel due to the higher profit margin. These price differences have, of course, also been recogonised by the Health Services of the individual Member States. Germany, for example, has imposed a quota on the volume of parallel imports the phamacists must dispense (SGB V, § 129 Abs. 1 No. 2 [3]). The Netherlands and UK use 'clawback' mechansims: any savings from the use of parallel imports are shared between the pharmacist and the government health authority [12].

3.1 Definitions & Legal Framework

A legal definition of the combined term "parallel imported medicinal product" (or a similar wording) can not be found in any binding legal act at Community level up to date. In fact, parallel import of medicinal products is neither explicitely explained nor regulated in community law.

However, parallel trade with medicinal products in Europe (including the EFTA states Iceland, Liechtenstein and Norway – together the EEA) does not lack legal basis. Parallel importation is based upon the fundamental principles of the Treaty establishing the European Community [13] - the 'free movement of goods' (Part II, Title 1, in particular Article 28 and 30). Whilst parallel imports are legal, there are certain limitations on the free movement of goods and on parallel trade which also apply to the goods "medicinal product". According to

Art. 30 of the EU Treaty, these may be restricted if they constitute a risk to the protection of the "health and life of humans" and to the "protection of industrial and commercial property".

As the past has shown, a 'medicinal product' is a product of special nature and hence needs specific regulations to effectively protect the public health. The Contergan catastrophe in 1964 was the driving force for the first European Directive on medicinal products [14]. Today, the community law on medicinal products is mainly represented by Directive 2001/83/EC as amended (and its implementations into national law) and the directly binding regulation 726/2004/EC. The specific provisions provided in these legislations and their relevance for parallel imports is discussed in the next subsection.

The second conflict to the principle of free movement of goods is the protection of industrial and commercial property (such as patents or trademarks). This provision would actually restrict parallel imports while the patent of the originator is valid. However, according to the jurisprudence of the ECJ [15], once a product has been placed on the market voluntarily in one Member State, it can not be prevented from being resold in any other Member State of the EU (known as the principle of "regional exhaustion of rigths") and the manufacturer no longer has any rights over what happens to the product. An exemption, however, has been agreed in the Accession Treaty for those products which remain unprotected by a patent in certain accession countries while they are still under patent in the old Member States of the EU (so-called 'special mechanism').

2.2 Regulatory framework for parallel imported medicinal products

In order to protect the public health, Article 6(1) of Directive 2001/83/EC as amended provides that no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued be the competent Authority. Generelly, this also applies to parallel imported medicinal products. As the requirements for a marketing authorisation for parallel imported medicinal products differ depending on whether the imported product in the country of exportation (where the product is bought by the parallel trader) has been granted either at national or community level, the following section is split.

Import of medicinal products, which have been authorised in accordance with Regulation 726/2004/EC – 'parallel distribution'

This special form of a parallel import is called **'parallel distribution'.** As a **c**ommunity marketing authorisation is, by definition valid the Community, no additional marketing authorisations are necessary in the individual Member States and the medicinal product automatically is and stays the same everywhere. Due to this fact, the Commission takes the view that parallel importers are not required at all to obtain an additional marketing authorisation for centrally authorised products [16] In this paper, however, parallel distribution is not discussed in detail as only the import of products authorised nationally is relevant.

Import of medicinal products which have been authorised from national authorities

If a medicinal product has not been authorised via a centralised procedure, nationally granted marketing authorisations exist in every Member State in which the medicinal product is marketed. Due to the history of marketing authorisation procedures, especially in case of older products, differences can exist between these marketing authorisations and hence between the products marketed in the individual Member States. Hence, from a formal point of view, the products have to be looked at as separate products which then require individual marketing authorisations when importing a product authorised in one country to another. As pointed out before, this usually involves the submission of a full dossier including results from pre-clinical, clinical and physico-chemical testing.

A parallel importer, however, does not have access to the detailed manufacturing and safety/efficacy data, as this information belongs to the intellectual property of the original manufacturer and thus could not obtain a marketing authorisation on his own. In favour of the EU principle on free movement of goods and with regards to the fact, that the products marketed in the different Member States by the original manufacturer probably not differ much, these strict regulatory rules have been migated by recent case law of the ECJ - particularly through the judgement in De Peijper (C-104/75) [17] and subsequent cases.

The regulatory framework formed by these cases is summarised in a "Commission Communication on parallel imports of proprietary medicinal products for which marketing

authorisations have already been granted, (COM/2003/0839 final)"[18] and is reflected below.

"A medicinal product may be imported in parallel on the basis of a licence granted according to a **'simplified' procedure** under which the applicant needs to provide less information that is required for a marketing authorisation. (…). In particular, when the information necessary for the purpose of protecting public health is already available to the competent Authorities of the Member State of destination as a result of the first marketing of a product in this Member State, a parallel import is subject to a licence granted on the basis of a proportionally simplified procedure provided that:

- The product will be imported from EU or EEA territory
- The imported product has been granted a marketing authorisation in the Member State of exportation (where the parallel imprter buys the product cheap), and
- The imported product is ***sufficiently similar*** to a product that has already received marketing authorisation in the Member State of destination"

Hence, the principle of parallel importation is, that a parallel import is considered as being already covered by a marketing authorisation in the importing Member State.

The conditions under which such an extention is possible obviously depends upon the level of similarity of the two products. In this context, the Commission Communication (as developed in the case Smith & Nephew and Pimecrown [19]) requires that the two products in question,

- do not have to be identical in all respects, but they
- should have at least been manufactured according to the same formulation
- using the same active ingredient and that
- they also have the same therapeutic effect.

With regards to the necessary level of 'sufficient similarity' the view presented in the Commission Communication and in the ECJ´s rulings are slightly different. Not included in the Commission Communication, but part of the judgement in Smith & Nephew and

Pimecrown, was the requirement of a common origin ("*that is, that their manufacturers are part of the same group of undertakings or, at the very least, that they produce those medicinal products under agreements with the same licensor" [paragraph 25])* which was further underlined by the ECJ in Rhone-Polenc Rorer and May & Baker [20]. Moreover, the ECJ´s ruling also differs from the Commission Communication with respect to the condition 'manufactured according the same formulation'. According to the ECJ in Rhone-Polenc Rorer and May& Baker , a parallel import application can also be granted, "*if ... the [parallel imported medicinal product] has the same active ingredients and therapeutic effect as the [medicinal product already authorised], but does not use the same excipient and is manufactured by a different manufacturing process ..."* [paragraph 48].

These deviations show, that the Commission Communication (even though being the only document available reflecting the view of the community) does not provide full clarification on this field of law. Therefore, also the national provisions of the individual Member States should be taken into account when assessing the regulatory framework for parallel imports. As these requirements have again been modified by another judgement in front of the ECJ (see next section), the individual national provisions will be discussed after having analysed this case (see section 5).

4 The Kohlpharma Case

As described in section 2, the legal framework for parallel imported medicinal products is mainly formed by case law of the ECJ. The latest case involving the regulatory aspects of parallel trade, namely the requirements for a parallel import marketing authorisation, is Case-112/02, known as the 'Kohlpharma Case', resolved by the ECJ in Luxembourg in April 2004 [1].

4.1 Main facts of the case – necessity of a 'common origin'

Background

The company Chinion Pharmaceutical Works Co. Ltd. ('Chinion'), established in Hungary, is a manufacturer of the active ingredient Selegeline hydrochloride. Chinion supplied this active ingredient to two companies: an Italian company called Chiesi Farmaceutici SpA ('Chiesi') and a German company called Orion Pharma GmbH ('Orion'). While Chiesi had a licence agreement with Chinion, Orion simply had a supply agreement with Chinion (with a supply chain directly to Germany or via Finland). Both companies used Chinion´s Selegeline hydrochloride independently from eachother in order to produce and sell an antiparkinson medicinal product. Chiesi marketed their product in Italy under the tradename 'Jumex' and Orion in Germany under the tradename 'Movergan'.

The issue

Kohlpharma GmbH ('Kohlpharma'), a German parallel importer, intended to buy Jumex in Italy and import it into Germany. For that Kohlpharma applied for a marketing authorisation for the parallel imported medicinal product Jumex at the BfArM under a simplified procedure so that they did not have to submit the extensive documentation required for a marketing authorisation for a new product (see section 2). But as Jumex is not marketed in Germany, Kohlpharma had to base the application upon the approval for 'Movergan' granted to Orion. The BfArM, however, objected the application citing the judgment in Case C-201 Smith & Newphew and Pimecrown, in which an application for a parallel import licence had been granted due to the fact that both manufacturers had a common origin (see page 14). Since Chiesi and Orion were unrelated companies, did not belong to the same group and did not

have a licensing agreement with the same licensor, the 'common origin' concept was not established for the BfArM.

Upon this, Kohlpharma appealed against the decision taken by the BfArM to the relevant Oberverwaltungsgericht (higher administrative Court), arguing that the ECJ did not establish the condition of a 'common origin' as a binding principle and what mattered only was whether the two products were substantially identical. The German Court then referred the case to the ECJ for a so called preliminary ruling in order to interpret this issue with regards to the EC Treaty (especially Articles 28 and 30). The specific question hereby referred to the ECJ by the German court is rather complex but according to paragraph 12 of the Kohlpharma judgement must be understood as: *"asking essentially whether, if the assessment carried out on the safety and efficacy of the medicinal product which is already authorised* [Movergan] *can be applied to the second product without any risk to public health, Art. 28 and 30 EC preclude the competent authorities from refusing to grant marketing authorisation to the second medicinal product* [Jumex] *with reference to the first* [Movergan] *solely on the ground that the two medicinal products do not have a common origin".*

The Decision:

Leaving aside the details of the Case, the answer to the above mentioned question given by the ECJ in the judgement on April 1, 2004 is the following:

"In the case where

- *an application for a marketing authorisation for a medicinal product is submitted with reference to a medicinal product that has already been authorised,*
- *the medicinal product which is the subject of the application ,is imported from a Member State in which it has obtained a marketing authorisation*
- *the assessment of safety and efficacy carried out for the medicinal product which is already authorised can be used in the application for a marketing authorisation for the second medicinal product without the risk to public health,*

Articles 28 EC et 30 EC preclude the application being rejected solely on the ground that the two medicinal product do not have a common origin." [Paragraph 21, holding]

4.2 A Closer Look inside the case

As the judgement of the ECJ is rather short and does not contain much legal reasoning, it seems – at first sight – that the issue has been solved properly and no questions remain unanswered. Hence, it should actually be possible to deduce the new regulatory rules for parallel imported medicinal products from the Kohlpharma judgement. However, upon closer examination, the Kohlpharma judgement creates even more uncertainty in this already complex area of law.

The original question discussed at the BfArM was whether it is possible to extend the marketing authorisation already granted for Movergan in Germany to the parallel imported medicinal product Jumex. Prior to the Kohlpharma Case, this was possible if the following conditions could be fulfilled (Commission Communication on parallel imports (COM/2003/0839 final, see also section 3.2):

- "The imported product [Jumex] has been granted a marketing authorisation in the Members State of exportation [Italy]

- The imported product [Jumex] is *sufficiently similar* to a product that has already received marketing authorisation in the Member State of destination [Movergan in Germany]".

With regards to "sufficient similarity", the Commission Communication requires that the two products in question, Jumex and Movergan, "*do not have to be identical in all respects, but they should have at least been manufactured according to the same formulation, using the same active ingredient and ... also have the same therapeutic effect*". As pointed out in section 3.2, the requirement of a common origin was not included in the Commission Communication, but was a basis in Cases Smith & Nephew and Pimecrown and Rhone-Polenc Rorer and May & Baker.

Conditions for a parallel import licence after the Kohlpharma case

As it seemed established in Smith & Nephew and Pimecrown, the BfArM´s argument to reject Kohlpharma´s application was that Jumex and Movergan did not have a common origin. Hence, all the following discussions and also the question referred to the ECJ for a preliminary ruling mainly focussed on the issue whether a 'common origin' is a binding requirement for a parallel import licence.

In this respect, the ECJ undoubtetly judged that a 'common origin' is not a binding condition. As required in the Commission Communication, the Court also held in its final decision that both the product of reference (Movergan in Germany) and the imported product (Jumex in Italy) have to have obtained a marketing authorisation:

"In Case where:

- *an application for a marketing authorisation for a medicinal product is submitted with reference to a medicinal product that has already been authorised,*
- *the medicinal product which is the subject of the application ,is imported from a Member State in which it has obtain marketing authorisation…"*

However, regarding the other criteria for 'sufficient similarity', namely that the two products, if not identical in all respects, should:

- use the same active ingredient,
- be (at least) manufactured according to the same formulation,
- have the same therapeutic effect,

the Kohlpharma judgement is not clear. This would, of course, not be of interest in case Jumex and Movergan are identical. However, as the composition of Jumex and Movergan differs, additional requirements are necessary to judge whether these two medicinal products are sufficiently similar. As an aside, even though no details on the composition of the two products can be obtained from the case, it is indicated in the wording of the question put to the ECJ for a preliminary ruling that with regards to the excipients the products do differ both qualitatively and quanititatively (see paragraph 8). This can also be confirmed by searching the official database from the BfArM and the world wide web (see table 1 on the next page).

Table 1

	Movergan	**Jumex**
Source	BfArM database (www.dimdi.de / AMIS/ öffentlicher Teil) (research conducted February 2006)	Jumex® patient information leaflet**
Product name	Movergan®	Jumex®
Marketing authorisation holder	Orion Pharma GmbH	Chiesi Farmaceutici SpA
Pharmaceutical form	tablet	tablet
Active ingredient	5 mg Selegilin hydrochloride	5 mg Selegilin hydrochloride
API supplier	Chinion Pharmaceutical Works Co. Ltd*	Chinion Pharmaceutical Works Co. Ltd
Excipients	Maize starch Povidone Magnesium stearate **Mannitol** **Microcristalline Cellulose**	Maize starch **Lactose** Povidone **Citric acid monohydrate** Magnesium stearate
* could not be confirmed **www.pianetasalute.com/Testi/FgIllustrtivi/prescrizione/19010.asp (original language italian)		

During the Case, only Advocate-General Tizziano defines conditions for 'sufficient similarity'. In his opinion, paragraph 51, delivered on 11 September 2003 [21], he states:

"The second [condition] is that the proprietary medicinal product, if not identical in all respects to a proprietary medicinal product already authorised in the Member State of importation, should be so similar to the latter that it can be considered to be essentially identical. This is the case, in particular, when those medicinal products contain, qualitatively and quantitatively, the same acitve ingredient, have the same pharmaceutical form, are bioequivalent, and do not appear, in the light of scientific knowledge, to differ as regard their safety and efficacy."

However, the ECJ did not follow the advocate-general´s opinion and did not include any special conditions with regards to the required degree of similarity between the products in

the decision - neither the ones defined by Tizziano nor the ones provided in the earlier Commission Communication.

Instead, the ECJ only requires that
"the assessment of safety and efficacy carried out for the medicinal product which is already authorised can be used in the application for a marketing authorisation for a second medicinal product without any risk to public health".

This very broad wording now leaves many questions unanswered. If two products do not necessarily have to have a common origin, is there any limitation for a parallel import except not to pose a risk to public health?

The ECJ obviously did not want to judge especially whether Jumex and Movergan can be regarded as 'sufficiently similar' and simply took as a basis *"the premiss that, for the purpose of assessing their safety and efficacy, the two medicinal products [Jumex and Movergan] do not differ significantly"*[paragraph 11]. However, by taking this for granted, the ECJ indirectely abandoned all previously established conditions or at least räumt ein room for interpretation whether these conditions still need to be fulfilled or not.

With the use of such broad terms, the ECJ also dissociates from the products in question, Jumex and Movergan, and thus indirectely accepts that decision is not limited to this special case. Hence, the decision could also be interpreted in the way that even medicinal products manufactured by unrelated companies and with an active ingredient obtained from a different source can be imported in parallel, even though Jumex and Movergan have the same active ingredient which is at least obtained from the same source (a common origin with regards to the the active ingredient).

Furthermore, when looking closer at the two products Jumex and Movergan, it seems rather strange, that they 'do not differ siginificantly' and that *"the assessment carried out on the safety and efficacy of the medicinal product which is already authorised [Movergan] can be applied to the second product [Jumex] without any risk to the protection of public health*".

Based upon Case 104/85 De Peijper, this would require that the authorities already *"have in their possession ... all the pharmaceutical particulars relating to the medicinal products in question ..."* This in turn would at least require that data is available which show that Jumex and Movergan can be used as equivalent products. When looking at Movergan and Jumex as "old " and "new" version (like a reformulation), the kind of data needed in order to safeguard public health can be derived from the "Commission Regulation No 1084/2004 concerning the examination of variations to the terms of a marketing authorisation" [22] and the "Guideline on dossier requirements for Type IA and Type IB notifications" [23].

As Table 1 on page 20 shows, the excipients of Movergan and Jumex differ qualitatively. Hence, a change from the composition of Movergan to the composition of Jumex or the way around, would at least require a type IB variation (as far as the different excipients can be regarded as being comparable). According to above mentioned guidelines, the following documentation needs to be provided in case of a change No. 18 (Replacement of an excipient with a comparable excipient):

- dissolution profiles of at least two pilot scale batches of the finished product comparing the new and old version (Jumex and Movergan),
- Justification for not submitting a new bioequivalence study according to the current "Note for Guidance on the Investigation of Bioavailability and Bioequivalence"[24],
- Data to demonstrate that the new excipient does not interfere with the finished product specification (and much more).

With regards to the justification for not submitting a new bioequivalence study, the relevant guideline in section 5.3 allows such a waiver only in cases *"where the bioavailability of the product undergoing change has been investigated and an acceptable correlation between in vivo performance and in vitro dissolution has been established"*. Furthermore, even though Jumex and Movergan have the same active ingredient manufacturer, the manufacturers of the finished product are different. Thus, also change No. 7 (addition of a manufacturing site) and No. 8 (change to batch release arrangements) would be necessary to be fulfilled, which includes i.a. the availablity of the following data: Batch analysis data and comparative data on the last three batches from the previous site and on the next two production batches on the new side (available upon request); method transfer from the old to the new side.

However, as Jumex and Movergan are marketed seperately in different countries by different marketing authorisation holders, it was never intended to replace one product by the other and

hence, there was never a need to generate those data. With this scientific background, it is therefore hard to understand how "*the parties to the proceeding and the national court appear to have no doubts as regards to those two conditions",* meaning that Jumex has been granted a marketing authorisation in Italy and that Jumex and Movergan do not differ significantly (see paragraphs 49-51 in the opinion of Advocate-General Tizziano).

Moreover, this immediatley raises the question how Kohlpharma could provide the necessary data to support their application. In this respect, the Court also present a new concept of 'burden of proof'. The ECJ held that it is for the importer to demonstrate based on available an accessible information that the imported product does not 'differ siginificantly' from the product already authorised [paralgraph 19]. However, where the importer "*does not have access to all the necessary information but provides data that make it at least plausible that the two products do not differ siginificantly for the purpose of assessing their safety and efficacy, the competent authority must act in such a way that their decision as to whether to extend to the second medicinal product the marketing authorisation granted to the first one is taken on the basis of the fullest information possible, including which is available to them or which they could have obtained through cooperation with the health authorities in other Member States*" [paragraph 20]. This obviously shifts the burden of proof from the applicant for a parallel import licence to the relevant regulatory Authority. The parallel importer now only needs to make it "at least plausible" that the parallel imported product does not differ siginificantly from the product already authorised (by information that is publically available such as the SmPC) and it is up to the regulatory authority to prove wheather this is not the case (see also section 6.1).

As pointed out at the beginning, when analysing the Kohlpharma ruling more closely, it appears that instead of providing clear and definite answers, it has created even more questions with regards to the conditions for parallel import licences. Hence, in order to clarify what is really possible in terms of parallel import applications, the next section focusses on the interpretation of the Kohlpharma decision by the individual national competent authorities.

5 National implementation of the Kohlpharma judgement

As the Commission Communication on parallel imports has not been updated since its last revision in December 2003 and no specific community act regulating parallel trade exists, there is no document available on Community level which could provide answers to the questions raised in the Kohlpharma case. Furthermore, the question remains whether and how the Kohlpharma judgement has been implemented by the individual Member States.

Therefore, this sections analyses the view of the individual Member States and how the national regultory authorities, especially the BfArM in Germany, have - if at all - implemented the Kohlpharma judgement. This evaluation should help to understand what the Kohlpharma case has really changed practically for parallel import applications.

5.1 Implementation in Germany

In general, the simplified procedure for parallel imported medicinal products is neither mentioned nor described in the German drug law (AMG) [25]. Only some sections indirectely include special provisions for parallel imports (e.g. under §10 exemptions for the blister labelling).

Information on the conditions and procedures for parallel imported medcinal products are provided in several guidance documents [26] which are, however, mostly relatively old and not easy to find. The most recent guidance document is called “Hinweise zum Parallelimport von Arzneimitteln” (guidance to parallel imported medicinal products) dated 19 August 2004, Version 05 (available in German only) [27]. This guidance paper summarises the documentation necessary to apply for a parallel import licence under a simplified procedure and provides some general information regarding this issue. Here, it is clearly stated that due to the Kohlpharma judgement, a common origin is not a binding principle anymore. A common origin can, however, be an importing factor when evaluating whether two products have the same therapeutic effect.

Above that, the guideline does not provide information on the other regulatory requirements. These can only found indirectly in a performance report of the BfArM ('Bewertungbericht zum Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)')" published in March 2004 [28]. Here, on page 37, it is stated, that the following criteria need to be fulfilled (translated from German):

- "The parallel imported medicinal product (PI), for which an application for marketing authorisation is submitted, is authorised in the Member State of destination (which is part of the EU/EEA),
- The PI is sufficiently similar to a medicinal product already authorised in Germany according the German Drug law (1976) ,
- The PI is manufactured from the same group of undertakings or under agreements with the same licensor as the reference product already authorised in Germany,
- There are no differences with regards to the therapeutical effects between the PI and product of the reference authorisation in Germany."

This section further provides clarification on the BfArM`s view of "same therapeutic effect". These conditions are based upon §29 (3) of the AMG, which is the paragraph for variations for those changes, that need an approval before the change can come into effect. Hence, the following differences are consideres to have a therapeutic effect and thus hinder a parallel import application to be granted:

- Differences in the active ingredient, both qualitatively and quantitatively;
- Pharamceutical forms which are not considered comparable,
- Different posology;
- Differences in the excipients, both qualitatively and quantitatively, in case bioequivalence needs to be provide;
- Differences in excipients (when falling under the excipients guideline).

As this report was issued shortly before the Kohlpharma judgement, the common origin here still is listed as a requirement.

However, this publication does not have any binding character and it is unclear whether these conditions still apply after the decision in the Kohlpharma Case.

From a seminar in Frankfurt in February 2006 [27], where a representative from the BfarM presented the regulatory requirements for parallel imports, the following seems to be required by the BfArM for a parallel import licence:

1.) The 'reference' product (RP) is authorised in Germany
2.) The parallel imported medicinal product (PI) is authorised in the country of origin
3.) The country of origin is part of the EEA
4.) The PI and RP are essentially similar
5.) The parallel importer and the marketing authorisation holder of the reference product are not related (see also section 5.2).

For the assessment whether the PI and the RP are essentially similar, the referee states, that both have to have the same active ingredient (qualitatively and quantiatively), the same excipients and the same pharmaceutical form. In case the excipients or the pharmaceutical form differs, bioequivalence studies or comparative in-vitro dissolution profiles are necessary.

With regards to burden of proof, the concept described in the Kohlpharma judgement is already included in one of the older guidelines regarding the simplified procedure for parallel imported medicinal products (Bekanntmachung des BMG über die Zulassung von parallelimporterten Arzneimitteln im Rahmen eines vereinfachten Verfahrens, section 3.3, dated Novermber 6, 1995 [26].

Again, the opinion given in this seminar can only be seen as an indicator of what might be required. No guideline has been published after the Kohlpharma case, which provides an united picture of all necessary regulatory requirements for parallel imported medicinal products.

5.2 Views of other EU/EEA members

Wheras the German point of view has been described above rather in detail, views of the other EU/EEA Members States are provided overleaf in tabulation. The main focus of this analysis is (provided that a guideline on parallel importation is available) whether the Kohlpharma provisions have been implemented and what the new requirements for a parallel import authorisations are.

The basis for the research was the information available on the homepages of the individual regulatory authorites (links are provided at www.heads.medagencies.org), however detailed references also provided in the tabulation. In case the homepage was not available in English, mostly no result could be presented.

As the individual Member States use slightly different terms when describing the regulatory framework for parallel imports, the following terms and abbreviates are used to provide a clearer picture (these terms will also be used in the following sections):

Parallel imported medicinal product (PI):	the medicinal product that is being imported in parallel from the country of exportation
Reference product (RP):	the product, which is authorised in the country of importation. Its marketing authorisation is used as reference authorisation for the PI in the simplified procedure (not to be confused with the definition of a 'reference medicinal product' in the context of generic medicinal products)
Country of importation:	country in which the PI is being imported an sold by the parallel trader
Country of exportation:	country in which the parallel trader buys the PI and exports it to the country of importation

Further abbreviaions used in the tabulation below:

MA = marketing authorisation

MAH = marketing authorisation holder

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Austria Austrian Drug Law. Paragraph 10c, Article 3.10 http://www13.ages.at/servlet/sls/Tornado/web/ages/content/7D34D71BCB097916C12570D5002C02BD	---	No conditions listed www.13ages.at/servlet/sls/Tornado/web/ages/content/7D
Belgium https://portal.health.fgov.be/portal/page?_pageid=56,513174&_dad=portal&_schema=PORTAL	Information on homepage (www.and Article 3, §2 of guideline on PI: "Arrete royal du 19 Avril 2001 relatif a l'importation parallele des medicaments a usage humain et a la distribution parallele des medicaments a usage humain et a usage veterinaire", (last update May 2004)	- Information and guideline available in French or Dutch only. - Published shorty after Kohlpharma judgement (common origin still seems to be a requirement)
Cyprus www.moh.gov.cy	**---**	-- page could not be found (technical error) --
Czech Republic www.sukl.cz	Guideline UST-28 "Approval procedure for parallel import of a medicinal product" published 6/2004	- No English version available - Published shorty after Kohlpharma judgement

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Denmark (DK) Danish Medicines Agency (DMA): Guideline on parallel import of medicinal products, June 2004 http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=3636	• RP shall have a MA in DK • PI shall be covered by a current MA issued by a country, which is part of EU/EEA • **The MAH for the PI in the country of exportation shall be identical with or belong to the same group of companies as the MAH for the RP in DK** • No differences of therapeutic significance between PI and RP	Guideline published after April 2004 - however Kohlpharma judgement not explicitely mentioned – common origin required in form of the MAH
Estonia Medicinal Products Act of 2005 (10 May 2005), § 66 http://www.sam.ee/orb.aw/class=file/action=preview/id=5118/EstonianAct-10May2005.doc	• Valid MA of the RP in Estonia • PI is by its clinical effects identical to a RP • PI is imported into Estonia from a MS of the EEA • PI has a valid MA in the MS of the EEA • PI and RP have same MAH or same manufacturer or belonging to the same group of manufacturers	Common origin (MAH or manufacturer) still required, Kohlpharma decision not implemented although publish after April, 2004

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**

Finland
 	
Regulation 7/2005 on parallel import of medicinal products, dated 9 December 2005
 	
http://www.nam.fi/english/legislation/administrative_regulations/index.html
	• Valid MA of RP in Finland
	• Valid MA in state from which PI is imported into Finland
	• Country of acquisition must be a member of EU/EEA
	• Similarity beetween the products is such that they can be considered as the same medicinal product:
	  • Therapeutic siginficance must not differ . the excipients of the products and/or their quantities may differ sligthly from each other e.g. a differrent colouring agent may be used
	  • **The marketing authorisation application may be rejected on the grounds that the two medicinal products do not have a common origin**
		Kohlpharma judgement not officially accepted even though guideline is issued 1 1/2 years after April 1, 2004.
		
		Finnish Authorities reserve the right to reject the applicaton if PI and RP do not have a common origin

France Guideline on PI:"Avis aux demandeurs d'autorisations d'importation parallel en France de specialites pharmaceutiques a usage humain", dated Mai 2004 : http://agmed.sante.gouv.fr/pdf/3/impparal.pdf	"…dont la composition qualitative et quantitative en principes actifs et en excipients, la forme pharmaceutique et les effects therapeutiques sont identiques a ceux d'une specialite pharmaceutique ayant obtenu une AMM deliveree par … l'agence francaise , a la condition que les deux specialites soient fabriquees par des entreprises ayant un lien juridique de nature a garantir leur **origine commune**"	- Guideline available in French only. - Published shorty after Kohlpharma judgement (common origin still seems to be a requirement)

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Greece www.eof.gr	---	- technical barriers concerning the greek font - English version of homepage available, however no guideline regarding PI could be found
Hungary www.ogyi.hu	---	No English homepage available
Iceland "Draft Regulation on parallel imported medicinal products", 22 November 2005 www.ministryofhealth.is	• Valid MA of RP when application is received • PI has MA in export country • Country of exportation is part of EEA agreement • **MAH of PI in export country is also MAH of RP in Iceland or member of same company or company group. If not, applicant shall demonstrate the same medicinal product is involved or that there is only a small difference*** • PI has same acitve ingredient, **same dosage form** and no difference in the effect of the medicinal product • *Small difference = difference in appearance, colour shape or flavour – provided that it is unimportant to its medicinal value	Common origin (referring to the MAH) still included as a main assessment criteria, however might no be a binding criteria

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Ireland Irish Medicines Board: "Guide to parallel product authorisations for medicinal products for human use", Edition 5, May 2004 http://www.imb.ie/uploads/publications/5734018_PPAGuidelinemay04.pdf	• RP in Ireland must have a current, full marketing authorisation at time of submission or, if not still authorised, it must have been withdrawn for commercial reasons only • **PI must be made by the same manufacturer or by a manufacturer belonging to the same group of companies as the Irish-market product or by a a manufacturer linked to the manufacturer of the Irish-market product by a contract with the same licencor** = common origin • PI must have the same active substances, the same pharmaceutical form and be identical to or have no significant therapeutic difference from the Irish-market product (RP) • The PI must be imported from an EU or EEA country • PI must have a current full MA in exporting state	• Reference is made to COM(2003)839 only • Kohlpharma judgement not implemented (date of issue of guide probably too close to Kohlpharma judgement) • Common origin still is a binding condition • Same pharmaceutical form as an additional condition
Italy www.ministerosalute.it	---	No English homepage available

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Latvia "Regulations regarding the Import, Export and Distribution of Medicinal Products and Requirements for the Opening and Operation of Medicinal Product Wholesalers", 22 April 2004 http://zaale.vza.gov.lv/english/likumdosana/narkotik.html	"8.1 Parallel importation … PI shall be released for free circulation in the exporting state, and they may be different from the corresponding medicinal product registed in Latvia in relation to which is performed parallel importation of the difference does no afftect ist therapeutic use (significance) and they conform to the requirements specified in these regulations"	- No detailed conditions for a PI listed - Not clear whether common origin still required. - Guideline published shortly after release of Kohlpharma judgement, hence the Regulations might not include the judgement
Liechtenstein www.liv.li	---	No guideline regarding PI could be found
Lithuana www.vvkt.lt	---	English version of homepage available, however no guideline regarding PI could be found
Luxemburg www.ms.etat.lu	---	No English homepage available
Malta Medicines Authority: "Guide to parallel importation of medicinal products for which marketing authorisations have already been granted", October 2004 http://www.medicinesauthority.gov.mt/parimport.htm	• RP must have a valid MA in Malta • PI must have same pharmaceutical form and be identical to or have no siginificant therapeutic difference form the Maltesian-market product (RP) • The PI must be imported from an EU or EEA country • PI must have a valid MA in country of exportation	• Reference is made to COM(2003)839 final • Kohlpharma judgement not mentioned

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
The Netherlands (NL) Medicines Evaluation Board: "Parallel-import authorisations", MEB-14-2.0, 8 April 2005 (in addition to 14-1.0) http://www.cbg-meb.nl/uk/docs/reghoudr/meb-14-v2_0.pdf.	• RP in NL must have a valid MA at time of submission of the PI authorisation application, PI must be authorised in country of exportation • Qualitative and qualitative composition of PI must be identical to that of the RP in terms of active substances • The pharmaceutical form of the PI must be identical to that of the RP Furthermore, 4 situations are described with regards to the qualitative and quantitative composition of the excipients and the manufacturer of the PI compared to the RP (for oral pharmaceutical forms only), which event. require the fulfillment of additional conditions: a) Composition of PI identical to RP and PI manufactured by the same manufacturer or a manufacturer that is a member of the same group of companies or a licensee of the manufacturer of the authorised RP ⇒ PI is acceptable b) Composition of PI **not** identical to RP and PI manufactured by the same manufacturer (see above) ⇒ PI is acceptable if the difference between excipients is so minimal that its bioavailablity (BA) is not expected to differ from that of the RP. A comparative dissolution study may be necessary in order to be able to reach a conclusion c) Composition is identical to RP and PI **not** manufactured by the same manufacturer (see above) ⇒ PI is acceptable if the dissolution profile is identical to that of the RP d) Composition of PI **not** identical to RP and PI **not** manufactured by the same manufacturer (see above) ⇒ PI is acceptable if its bioavailablity is identical to that of the RP	- **Kohlpharma judgement has been implemented (see introduction) and even further defined**. - **Common origin** **is not a binding requirement – however additional data required if common origin is not established (vorlage von comparative dissolution studies or even BA studies).** - **Burden of proof** **seems to be more on side of the applicant**. Even though the MEB indicates that if the applicant has no access to the requested data, the MEB must obtain them from the regulatory authorities, the wording in the Kohlpharma judgement (that the applicant has to "make it at least plausible that the two products do not differ siginifcantly") has not been adopted The Guideline rather requires that : "the applicant must provide the following information (…). It may be necessary to carry out a comparative dissolution study or a bioequivalence study". - **Same pharmaceutical form as an additional condition** - **Difference in exipients or manufacturers only acceptable for oral pharmaceutical forms**

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Norway www.legemiddelverke.no	---	English version of homepage available, however no guideline regarding PI could be found (only an application form)
Poland www.bip.urpl.gov.pl	---	No English homepage available (According to the article "Parallel importation of medicinal products under EC and Polish Law" by Magdalena Bartosik in "The Warsaw Voice" in May 2005, it can be deduced, that common origin still is a requirement in Poland: "This ruling is particularly important in view of the fact that the Polish Pharmaceutical Act apparently runs contrary to it".)
Portugal www.infarmed.pt	---	-- page could not be found (technical error) --
Slovac Republic www.sulk.sk	---	English version of homepage available, however no guideline regarding PI could be found
Slovenia www.mz.gov.si	---	English version of homepage available, however no guideline regarding PI could be found
Spain http://www.agemed.es/actividad/legislacion/espana/docs/RCL_2000_2463Vigente2005-1.pdf	Guideline: "Real Decreto 1785/2000, Sobre la circulation intracomunitaria de medicamentos de uso humano, 28 october 2000"	- Guideline available in Spanish only. - published before Kohlpharma judgement

EU/EEA member Source	**Conditions for a PI licence**	**Implementation of Kohlpharma / comments**
Sweden (SE) „The Medical Products Agency´s (MPA) Provisions and Guidelines for Marketing Authorisation of Parallel imported Medicinal Products", (LVFS 2004:8) published 22 April 2004 http://www.lakemedelsverket.se/Tpl/NormalPage____2180.aspx	• The RP shall have a MA in SE when the PI application is submitted to the MPA for the first time • PI shall have a MA in the country of exportation • Exporting state shall be a member of the EU/EEA • PI shall be sufficiently similar to the RP Minor differences accepted e.g. concerning colour, scoring, dosage form, size, excipients and manufactuirng process. **"In this assessment attention is paid to, e.g. whether the PI and the RP have a common origin and contain the same active ingredient and also that they have the same therapeutic effect" (common origin refers to MAH or manufacturer).**	- The Guideline has been adopted 31 March 2004 – before the official closure of the Kohlpharma judgement and has not been updated since then - Common origin (same MAH or same manufacturer) therefore part of the assessmenr, but (even before the Kohlpharma judgement), not a binding principle.
United Kingdom (UK) http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=105		Information on homepage and an application form (dated April 2004 –before or at the same time as the Kohlpharma judgement) available - No guideline regarding PI could be found which reveal necessary requirements

From the evaluation provided on the previous pages, it can be seen that a lot of Member States have established national provisions for the parallel import of medicinal products.

However, the most guidelines (in Belgium, Czech Republic, Denmark, France, Ireland, Latvia, Spain, Sweden and United Kingdom) were issued before or shortly after the Kohlpharma decision and hence do not include the new provisions

Other Member States (Estonia, Finland, Iceland) have not implemented the Kohlpharma decision even though their Guidelines are published a lot later.

Only Germany and the Netherlands did implement the Kohlpharma Case and especially the Dutch Guideline (MEB-14-2.1) lists detailed requirements for parallel import applications.

Hence, when assessing the question whether generic medicinal products can be imported in parallel, this guideline will be taken as a basis (see next section).

6 Parallel import of generic medicinalproducts- possible impacts of the Kohlpharma Case

"Now that common origin is not a prerequisite, we may see many generics entering the local market as PI´s. All they will need to demonstrate is the appropriate level of similarity to the locally authorised product. The burden of proof is shifted to the Authority to show a significant difference from the local product or the importation would have to be allowed, without the need to apply for a separate marketing authorisation." [29]

"The Case is likely to lead to uncertainty and potentially an increase in the scope for parallel trade, as it blurs the distinction between the rules on marketing authorisations for generic products and the rules governing parallel importation". [30]

As the above listed citations from articles written on the Kohlpharma Case reveal, that the judgement does raise an interesting issue with regards to generic medicinal products and the next case to be argued before the ECJ could be one where a parallel import application is submitted for a generic medicinal product with reference to the originator product.

The following section therefore evaluates whether such an application could really be successful under the current marketing authorisation rules, where the limitations are and what advantages such an application would actually have.

6.1 Possiblities and limitations gaining a parallel import authorisation for generic medicinal products

As described in the previous sections, until April 2004, case law required that a parallel imported medicinal product could only be granted a marketing authorisation if there was a link between the manufacturers of the local product and the imported product, either because they were companies in the same group or obtained the product from a common licensor. Under these circumstances, a generic parallel import application would have not been possible at all, as in case of a generic product neither the active ingredient nor the finished product is obtained from the same source (see section 2.1). However, the concept of 'common origin' was removed as a result of the Kohlpharma case and therefore did pave the way for such a scenario.

In order to evaluate whether a generic medicinal product could be granted a parallel marketing authorisation, the conditions listed in the Kohlpharma judgement (see below) need to be compared to the requirements for generic medicinal products:

(1) An application for a marketing authorisation for a medicinal product is submitted with reference to a medicinal product that has already been authorised;
(2) The medicinal product which is the subject of the application is imported from a Member State in which it has obtained a marketing authorisation;
(3) The assessment of safety and efficacy carried out for the medicinal product which is already authorised can be used in the application for a marketing authorisation for the second medicinal product without the risk to public health.

With regards to condition (3), the Kohlpharma judgement does not provide any details under which circumstances this can be the case - it is only required that the medicinal product to be imported 'does not differ significantly' from the medicinal product that is already authorised (see also section 4.2).

In order to avoid any speculations with regards to the required degree of similarity between the two product, that the ECJ might have or not have established in the Kohlpharma case, rather the conditions established in the Dutch guideline MEB-14-2.0 (see page 34) should be

used as a basis for the following evalutions (see also section 5.2). Hence, the conditions that need to be fullfilled in addition to (1) and (2) are:

(3a) The qualitative and qualitative composition of the product to be imported must be identical to that of the reference product in terms of active substances;

(3b) The pharmaceutical form of the product to be imported in parallel must be identical to that of the reference product*.

[*As pointed out on page 27, the term 'reference product' used in the Dutch Guidelinenshould not be confused with the definition of a 'reference medicinal product'as defined in Article 10 (2) (a) of Directive 2004/27/EC]

Moreover, the guideline lists other requirements depending on whether the composition of the two products (imported and reference product) in terms of the excipients is identical, and whether the manufacturers of the imported and reference product are the same or members of the same group of companies or have a licensing agreement with the same licensor. As generic medicinal products are produced and supplied by companies other than the one that held the original patent and usually have a different composition with regards to the excipients (at least qualitatively – as the other information is confidential), conditions (b,2) listed in the Guideline MEB-14-2.0 need to be fulfilled:

(3c) The product to be imported in parallel is acceptable if its bioavailablity is identical to that of the reference product (for oral pharmaceutical forms only)

In the following, these conditions will be applied to two scenarios:

- Scenario 1:
  Is it possible for a parallel trader to import a generic medicinal product (authorised in the Member State of exportation only) with reference to the originator product (authorised in the country of importation) under the simplified procedure?

- Scenario 2:
  Is it possible for a generic company to import its own generic medicinal product (authorised in the Member State of exportation only) with reference to the originator product (authorised in the country of importation) under the simplified procedure?

Scenario 1: Is it possible for a parallel trader to import a generic medicinal product (authorised in the Member State of exportation only) with reference to the originator product (authorised in the country of importation) under the simplified procedure?

Condition (1):

An application for a marketing authorisation for a medicinal product is submitted with reference to a medicinal product that has already been authorised.

According to Art. 6 of Directive 2001/83/EC as amended, no medicinal product may be placed on the market of a Member State unless a marketing authorisation has been issued by the competent authority of the Member State where the product is marketed. Hence, in case the originator product is marketed in the country where the parallel importer whishes to obtain a parallel import authorisation, above mentioned conditions should be fulfilled.

Problems could, however, occur in case the corresponding condition in the Dutch Guideline, MEB-14-2.0, needs to be fulfilled. Here, the wording is slightly different:
"Reference must be made to a reference product that is authorised in the Netherlands. This reference product must have a valid marketing authorisation at time of submission of the parallel import authorisation application."
Actually, this provision is rather an advantage than a disadvantage, as it enables parallel importation, even though the marketing authorisation of the originator product has been withdrawn after the parallel import application is submitted (provided that the reasons for the withdrawal are not related to the protection of public health, see Cases C-172/00 Ferring [31] and C-15/01 Paranova [32]). Nevertheless, it still has to be checked by the parallel importer that the marketing authorisation of the originator product is valid - at least at time of submission. In Germany, for example, a medicinal product can still be on the market for another 2 years, even though the marketing authorisation holder has already rennounced the marketing authorisation for the originator product (German Drug Law, §31 (4)). In such a case, it is not assured that the authorities would regard the authorisation as being still valid. Some Member States offer databases in which the licencing status can be checked (e.g. AMIS database in Germany [33]).

A further issue, that should be mentioned in context of this condition, is not listed in the Dutch guideline, but can be fould in the Irish "Guide to parallel product authorisations for medicinal products for human use" (see also section 5.2). In this guideline, the relevant condition is worded as follows: *"The reference product in Ireland must have a current,* ***full*** *marketing authorisation at time of submission or, if not still authorised, it must have been withdrawn for commercial reasons only"*. The authorisation of the reference product therefore has to be based upon a 'full' respectively complete dossier in accordance with the provisions of Article 8 (hence based upon a full documentation including results of pharmaceutical, pre-clinical tests and clinical trials - as required for a 'reference medicinal product' in the context of generic medicinal products). Even though this is not relevant for our scenarios (as originator products usually contain all relevant information regarding the medicinal product), such a requirement would certainly preclude parallel import applications with reference to generic medicinal products. Such a provision can also be found in the rules for generic applications. In Chapter 1 of the Notice to Application Volume 2A, dated November 2005, it is clearly stated: "*On the contrary, the dossier for a generic application does not contain all relevant information concerning the medicinal product. Therefore, a generic application refering to a generic dossier is not possible*" [34].

Condition (2):

The medicinal product which is the subject of the application, is imported from a Member State in which it has obtained a marketing authorisation.

This condition in fact includes two provisions. The first one requires, that the country from where the medicinal product is imported is a Member State of the EU. In most guidelines published by the different Member State, this provision is extended to the EEA (EU Member States plus Norway, Iceland and Liechtenstein). Hence, it is not possible to take advantage of the simplified procedure if the product is imported from outside the EU or EEA.

Secondly, this condition implies, that the parallel imported product needs to have obtained a marketing authorisation in the country of exportation. Even though the product to be imported in our scenario is a generic medicinal product, it still needs to have obtained a marketing authorisation before it can be marketed (see section 2.2). Therefore, a generic medicinal product marketed in the EU or EEA does fulfill this condition.

Conditions (3a) and (3b):

The qualitative and qualitative composition of the product to be imported must be identical to that of the reference product in terms of active substances. The pharmaceutical form of the product to be imported in parallel must be identical to that of the reference product.

As described in section 2.1 and defined in Article 10 (2) (b) of Directive 2001/83/EC as amended, a generic medicinal product is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference product and whose bioequivalence with the 'reference medicinal product' has been demonstrated by appropriate bioavailablity studies. Furthermore, the second and forth subparagraph of this Article defines the terms 'same active ingredient' and 'same pharmaceutical form' as follows:

"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivates of an active substance shall be considered to be same active substance, unless they differ significantly with regard to safety and efficacy. (...) The various immediate release oral pharmaceutical forms shall be considered as being one and the same pharmaceutical form".

Therefore a generic medicinal product can consist of a slightly different active ingredient (e.g. metoprolol tartrate) and pharmaceutical form (e.g. tablet) than the originator product (e.g. metoprolol succinate, film-coated tablet). When reading the conditions (3a) and (3b) closely, the Dutch Medicines Evaluation Board, however, requires both products to be 'identical' – not just to be the 'same'.

This very strict requirement in the Dutch guideline may, however, be challengeable in front of the ECJ as, one the one hand, this would run contrary to the current Commission Communication on parallel imports (which only requires that the two products use the 'same' active ingredient). On the other hand, even if the salts would differ, it is excluded by definition of Article 10 (2) (b) of Directive 2001/83/EC as amended, that the active ingredients would differ signifcantly.

Nevertheless, it can not be ruled out, that only generic medicinal product with *identical* active ingredients (identical salts, ethers, etc.) and *identical* pharmaceutical forms are candidates for parallel importation.

Condition (3c):

The product to be imported in parallel is acceptable if its bioavailablity is identical to that of the reference product (for oral pharmaceutical forms only).

As mentioned at the beginning of this section, this conditions needs to be fulfilled, because generic medicinal products usually have a different composition in terms of the excipients and are manufactured by a different, independent manufacturer compared to the originator product. In this case, the Dutch guideline only allows the parallel importation of medicinal products which are oral pharmaceutical forms. Hence, the parallel import of a generic product with a pharmaceutical form other than one administered orally (e.g. a locally acting pharmaceutical form such as a dry powder inhalor) will probably not be successful under the Dutch rules. This restriction seems reasonable at least for locally acting products, as therapeutic equivalence for these products can not be demonstrated by bioavailability resp. bioequivalence studies. As explained in the "Note for Guidance on the investigation of bioavailability and bioequivalence", section 5.1.8, *"products for local use (after oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration) intended to act without systematic absorption, the approach to determine bioequivalence based on systemic measurements is not applicable and comparative clinical studies are in principle required"*.

Hence, for generic medicinal products, which are oral pharmaceutic forms, the parallel trader needs to submit a bioequivalence study, which shows that the bioavailablity of the generic product is identical to that of the product already authorised in the country of importation.

However, is a parallel importer in the position to provide results of a bioequivalence study or even conduct bioequivalence studies?

According to the EU Clinical Trials Directive (Dir. 2001/20/EC) [35] an authorisation has to be given in order to test a medicinal product on humans. This also applies to bioequivalence studies. In order to receive such an authorisation, the applicant (in this case the parallel importer) would have to submit data on the Investigational Medicinal Product (IMP, here the generic medicinal product) to the health authority in the country where the trial is to be carried out. Additionally, the Ethics Committee where the trial is to be located needs to give its approval. In case of a bioequivalence study such an application includes i.a. the submission

of an Investigational Medicinal Product Dossier (IMPD), which contains information on the quality of the IMP, e.g. composition, pharmaceutical development, batch manufacturing formula, description of the manufacturing formula, specifications, certificates of analyses of a batch of the IMP etc. In other words, a parallel importer, who only buys the products at a wholesaler in the country of exportation, does not have the necessary knowledge of the medicinal product to conduct bioavailablity studies.

For this case, the Kohlpharma judgement (C-112/02, paragraph 20) and the Dutch guideline (MEB-14-2.0, page 3) provide an alternative: If the applicant, has no access to these data (e.g. results of bioequivalence studies), but provides data that make it at least plausible that the two medicinal products do not differ siginificanty, the compent auhtority must obtain them from the Member State from which the product is to be exported (see also dection 4.2). Would this be a realistic option for a parallel trader to receive a parallel import authorisation for a generic medicinal product?

The success depends upon two factors: First of all, the parallel importer needs to show, that it is plaubsible that the parallel imported product (in this case the generic product) and the product already authorised in the country of import (the originator product) do not differ significantly. Secondly, the required information proving that the two products in question do not pose a risk to public health, needs to be available at the competent authority where the generic medicinal product has originally been authorised.

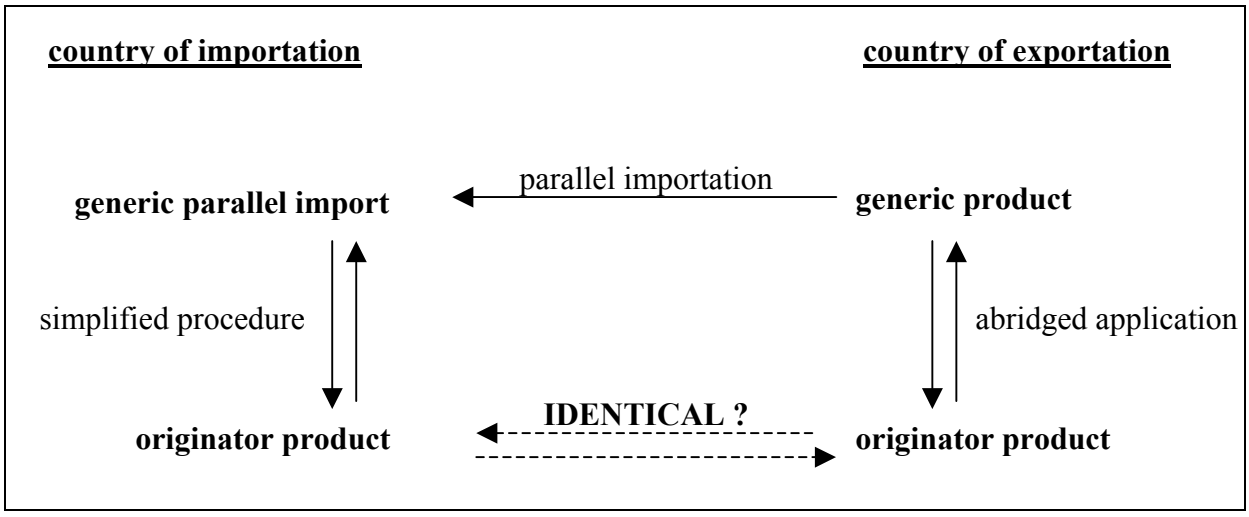
Plausible argumentation

Both provisions, the Kohlpharma judgement and the Dutch guideline, do not provide any further clarification on what exacetly the parallel importer needs to provide in order to make a plausible argument - which does not have to be a disadvantage. In this way, any information might already be sufficient to shift the burden of proof to the authorities. However, the finished product, which the parallel trader buys from the wholesaler, already contains various information (i.e. quantitative and qualitatative composition of the active ingredients, qualitatative composition of the excipients, appearance of the tablets) which the parallel trader can use as arguments when comparing these to the originator product. In case the excipients (at least qualitatively) are the same, the parallel trader should already have a strong argument that the generic medicinal product and the originator product do not differ signifcantly.

Furthermore, many generic companies in Germany include information on the conducted bioequivalence study in their SmPC (with pharmacokinetic data on C_{max}, t_{max}, AUC, confidence intervals and plasma profiles comparing the test and reference product), which is published on their homepage in the internet (e.g. www.hexal.de, www.stada.de or under www.fachinfo.de). Even though, the name of the reference medicinal product is usually not mentioned in these publications, such a information should at least be a sufficient indicator, that the products do not differ signifcantly - also if the excipients differ. As the bioequivalence study is available to the authority where the parallel import application is made, the Authorities can check whether the reference product is acceptable (see below).

Information available to the competent Authority

If a parallel importer now made a plausible argument that the parallel imported generic product does not differ signficantly from the originator product, the regulatory authority has to prove that the generic product does not pose a risk to public health. Hence, as required in the Dutch guideline, bioavailability studies must be available showing that the parallel imported generic product and originator product in the country of importation are bioequivalent. When looking at the chart below, it could be a problem that this information really is available at the authorites:



In the country of exportation, where the generic product originally was authorised via an abridged application, bioequivlaence studies are probably available comparing the generic product and originator in the country of exportation only. If this is the case, the results of the study are only transferable to the parallel import application if the originator product in the

country of exportation is identical to one in the country of importation. This would surely be the case if the originator product was approved in both countries via a mutual recognition or decentralised procedure. If the originator products were authorised at a time, when parallel national submission were still allowed, additional results from in-vitro dissolution testings comparing the two originator products would be necessary.

This implies, that the success of a generic parallel import application mainly depends upon the information that is available at the competent Authorities in the country of exportation and whether the originator product in both countries (importation and exportation) is identical. The parallel trader can not adequately support such an application and is mainly dependent on the authorities.

Other factors limiting the parallel import of generic medicinal product

Compliance with the dosage recommendations

The Dutch Guideline also requires that the imported product can fully comply with the dosage recommendations given in the SmPC for the Dutch reference product. Hence, it might be a problem in case the generic product does not have a breakline wheras the originator product is scored. If a lower strength of the parallel imported generic product is available to realise, for example, the initial dose, the application might be acceptable. However, if no lower strength is available and the dosage recommendation can not be realised with the parallel imported generic product, the application is likely to be rejected.

Pack sizes

In order for a parallel import to be exchangable with an origintor product, especially with regards to reimbursement policies, it should have the same pack sizes as the originator product . In case the pack size in the country of export differs from the country of import, the pack size needs to be amended manually – if at all possible (e.g. blister strips might need to be cut in parts). In many cases, this does not hinder a parallel importation, however needs to be taken into account, when parallel importing the product.

Patents

When originator products are being imported in parallel, patents are not relevant. In this case the principle of 'regional exhaustion of rights' comes into effect, which implies, that once a product has been placed on the market voluntarily in one Member State, it can not be prevented from being resold in any other member state of the EU. However, in case of generic medicinal products the principle of 'regional exhaustion of rights' is not valid as the active ingredient and the finished product are manufactured by different undertakings which do not have a relationship to the origiator product. Therefore, even though a parallel import licence may be granted, the active ingredient or other particulars of the medicinal product might still be protected by a patent or Supplementary Protection Certificate and thus can only be imported in case the patents are expired.

Scenario 2: Is it possible for a generic company to import its own generic medicinal product (authorised in the Member State of exportation only) with reference to the originator product (authorised in the country of importation) under the simplified procedure?

This scenario does not differ whith regards to conditions (1), (2), (3a), (3b) and the other possible limitations presented above. However, with regards to condition (3c), the situation here is different:

Condition (3c):

The product to be imported in parallel is acceptable if its bioavailablity is identical to that of the reference product (for oral pharmaceutical forms only).

Contrary to the parallel importer, a generic company does have the necessary knowledge of the medicinal product in question and is thus in the position to perform bioequivelence studies with the appropriate reference medicinal product (from the country of import). Hence, for a generic company, it should not be a problem submitting the necessary information to the authorities and, in case the results show that the two products are bioequivalent, to receive a parallel import authorisation.

This seems so simple, that the question arises, why we don´t already see many generics entering the local markets as parallel imports? Hence, there must be a provision in the current rules which hinder or at least make it difficult for a generic company to take advantage from the simplified procedure.

When reviewing Directive 2001/83/EC as amended, Article 17 subparagraph one and two may provide such a limitation:
"(...) Applications for marketing authorisation in two or more Member States in respect of the same medicinal product shall be submitted in accordance with Articles 27 to 30.
2. Where a Member State notes that another marketing authorisation application for the same medicinal product is being examined in another Member State concerned shall delince to assess the application and shall advise the applicant that Articles 27 to 30 apply "

Articles 27 to 30 describe i.a. the mutual recognition procedure (MRP). Hence, the provisions in Article 17 indirectly make the MRP compulsory when the same applicant wishes to place the same product on the market in more than one Member State. This obligation is also reflected in the 'Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 220/03)`, where it is stated in section E2:
"This means that from now on, any medicinal product which is to be place on the market of more than one Member State has to be processed through the mutual recognition procedure only".

On the other hand, these provisions originally were set up not to prevent parallel importation. They were established rather to avoid independent national procedures, which had been possible until 31 December 1997 (see argumentation in the Commission Comunication mentioned above). It is therefore not clear whether these provisions can really be used to reject a parallel application.

Anyway, there is way to by-pass the obligation of performing a MRP. In the MRFG Question and Answers document [36], the following is included:

"When a company has sold the dossier for a medicinal product to an unrelated company, is it possible for both Companies to apply nationally for marketing authorisation in different Member States?

***ANSWER**: Yes, they should both apply nationally in any Member State (the same or different) and afterwards initiate a mutual recognition procedure if they intend to market the medicinal product in more than one Member State, unless they can be considered as the same applicant (as defined in Question 78). Is is not possible to start a mutual recognition procedure for a different applicant, even though the dossier is the same."*

Hence, if the generic company would, let´s say, 'make the information, which is necessary for a parallel import application, available to an 'unrelated company'*, the obligation to enter a MRP would not come into effect.

Futhermore, another argument against this scenario could be, that the simplified procedure might only be used when the information necessary to apply for a marketing authorisation via a 'normal" application (e.g. an abridged application) is not available to the applicant. To evaluate whether such an argument is a knock-out for generic parallel import application, one needs to go back to the beginning of parallel importation (see also section 3), hence to the judgement in De Peijper:

"That was the effect of the Court´s judgement in Case 104/75 De Peijper [1967] ECR 613, paragraphs 21 and 23, which stated that, if the public health authorities of the Member State of importation already have in their possession, as a resultt of importation on a previous occasion, all the pharamceutical particulars relating to the medicinal product in question ... it is clearly unnecessary, ... to require a second trader ... to produce these particulars again"

* According to the Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 220/03), two or more companies are considered to be the same applicant, when they belong to the same mother company or group of companies, have concluded agreements (e.g. 'licensees') or exercise concerted practices concerning the placing on the market of the relevant medicinal product in the different Member States.

From this paragraph, the above mentioned argument can not really be confirmed. The wording in De Peijper does not exclude that an applicant can have the necessary information - the authorites can just not require an applicant to produce these informations again.

As discussed above, the problem of scenario 2 is not the availablity of the relevant data to assess whether the generic imported product and the originator product are the same. It rather is the view of the regulatoy authorties and whether they allow a generic company to make use of the simplified procedure. At least through the by-pass of a ‘neutral’ applicant (who would act on behalf of the generic company), one problem, that would actually rule out this possibiliy, could be solved.

In the end, it particularly depends upon the kind of generic product that is to be imported in parallel. Certain products (e.g. inhalors, systemic patches) will most likely not be appropriate candidates for such a scenario. But an application for a products that has the identical (!) active ingredient, same appearance, and oral pharmaceutical form as the originator product and for which a ‘neutral’ applicant can submit the necessary bioavailability data showing that the generic parallel import and the originator are bioequivalent, could be successful and for will for sure keep the ECJ busy.

6.2 Advantages of a generic parallel import application

Parallel imported products usually need to be relabelled or repacked in order to be effectively marketed in the importing country. This is mostly necessary because the patient information leaflet or the information on the carton need to be translated. Hence, the product as such does not look very nice after such a procedure (stickers on the package etc.). Furthermore, as section 6.1 has shown, there still remains some degree of uncertainty whether a generic parallel application would be accepted by the regulatory authorities. Hence, why should anyone want to import a generic medicinal product in parallel?

In Table 3 (see next page), the major effects of either applying for a parallel import (PI) authorisation via the simplified procedure or submitting an abridged application via the mutual recognition procedure (MRP) are compared. As an example, the provisions layed down in the "Hinweise zum Parallelimport von Arzneimitteln" (guidance to parallel imported medicinal products) dated 19 August 2004, Version 05 (available in German only) [27] is compared to the provision layed down in Directive 2001/83/EC as amended

Some advantages, the simplified procedure involves, are already obvious from this tabulation (e.g. less documentation, lower fees, shorter assessment times). Some aspects, however, need be discussed in more detail.

Table 3	**PI application / simplified procedure**	**Abridged application / MRP**	**Comments**
Content of the application	• Cover letter and table of contents • declariation on the special mechansim (see section 3.1) • equivalent of Module 1 containing - application form, manufacturing authorisation of the parallel importer, - information on the reference product (e.g. picture of the package, description of the pharmacetuical form and its appearance, current pil and SmPC), information on the parallel import (see reference product), text proposals for the parallel import (needs to be identical to the ones authorised for the reference product) • argumentation the make it plausible that the imported product and the reference product do not differ siginficantly or results of bioequivalnce studies[1]	• Module 1 • Module 2 (quality overall summary, non- clinical and clinical overview) • Module 3 (Quality) • Module 4 (if applicable) • Module 5 (bioequivalence study, literature references)	PI application less complex, does not include data on the quality of the product and does not need to provide expert statements (see Module 2)
Assessment time	Ideally 45 days (realistic 7 months) [27]	MRP: 90 days + national phase	Shorter assessment times for PI
SmPC, pil	Identical to the originator	Vertical disharmonisation	**see evaluation below**
fees	2934 Euro [2]	15.843[1]	Significantly lower fees
Intellectual property rights (IPR)	• Patents (if product is generic, otherwise principle of exhaustion of rights) • Trademark issues (only in case of originator products)	• Data protection • Patents • Usually no trademark issues	No data protection for parallel imports, **see evaluation below**

[1] BfArM-Kostenverordnung, version dated 10.12.2003

[2] "Hinweise zum Parallelimport von Arzneimitteln" (guidance to parallel imported medicinal products) dated 19 August 2004, Version 05

SmPC and pil of the generic resp. the parallel import versus the originator product

As both products, generic and parallel imported medicinal product, should be therapeutic equivalents to the originator product, it is very important for the success of the product that the SmPC and pil are identical to that of the originator product (at least the key sections concerning indications, posisology, contraindications). If the SmPCs are not identical it can limit or prevent the products from being included in lists allowing substitution or reimbursement, which in turn results in a major loss of profit.

Generic medicinal products

In case of a mutual recognition procedure (MRP), the applicant enters the MRP with a SmPC identical to the one originally authorised in the Reference Member State (RMS). The SmPC and pil authorised in the RMS have, in turn, been approved on the basis of the approved texts of the originator product marketed in the RMS.

During the assessment, the CMS usually check the content of SmPC against their local originator SmPC. Until 1998, marketing authorisation rules still allowed independent national procedures, which resulted in a different assessment of the same product in the various Member States. Hence, the SmPCs (e.g. indications, posology, warnings) of the originators often differs between Members States. In this case, the Member States often are unwilling to accept any differences between the SmPC of the originator in their country and the generic SmPC. Therefore, the generic SmPC will usually be compromise of the various SmPC versions in the CMS, resulting in a so-call ‘horizontal harmony’, but ‘vertical disharmony’, because the SmPC of the originator and the generic differs within a country [8]. If no consensus can be reached, this conflict can even lead to costly and time consuming arbitration procedures.

An example for such a ‘vertical disharmony’ is the SmCP for gabapentine 300 mg capsules. As it is obvious from the tabulation below (Table 4), the indications of the originator in Germany (Neurontin 300 mg Kapseln) and the generic (Gabapentin Stada 300 mg Hartkapseln), which was authorised through a MRP, differ:

Table 4

	Neurontin 300 mg Kapseln licence no.: 47275.01.00 SmPC dated Juni 2005*	**Gabapentin Stada 300 mg Hartkapseln** licence no.: 62744.01.00 SmPC dated: October. 2005*
section 4.1 indications	Epilepsie: **Monotherapie** (einschließlich Erstbehandlung) bei Erwachsenen und Kindern über 12 Jahren mit einfachen und komplexen partiellen Anfällen mit und ohne sekundäre Generalisierung. Zusatztherapie bei Erwachsenen und **Kindern ab 3 Jahren** mit partiellen Anfällen mit und ohne sekundäre Generalisierung. Neuropatische Schmerzen : Zur Behandlung von neuropatischen Schmerzen im Erwachsenenalter	Als Zusatztherapie bei partieller Epilepsie mit oder ohne sekundär generalisierten Anfällen bei Patienten, die auf eine Standard-Antiepileptikatherapie nicht ansprechen. Zur symptomatischen Behandlung postherpetischer Schmerzen
Section 4.2, children	See above	**Kinder (<12 Jahre)** Wirksamkeit und Unbedenk-lichkeit sind in dieser Patientengruppe bis jetzt **noch nicht** nachgewiesen worden
*Source: www.fachinfo.de		

The generic product, Gabapentin Stada 300 mg Hartkapseln, does not include the monotherapy in epilesy (‘Monotherapie’) and can only be used for children over 12 years of age, whereas the originator in Germany provides a dosage scheme for pediatric patients aged 3-12 years.

As pointed out above, such a ‘vertical disharmony’ may have major consequences for the substitution or reimbursement of the generic medicinal product.

Parallel imported m edicinal products

The priniciple of the simplified procedure for parallel imports is, that the existing marketing authorisation for the originator product is being extended to be the parallel imported product (see section 3.2). Hence, also the contents of the SmPC and pil are automatically valid for the parallel imported product. This can be reaffirmed in various guidelines on parallel importation in Member States of the EEA (see table 5 overleaf).

Table 5

Country in EU/EEA Source	**Requirements for the pil and/or SmPC for the parallel import (PI)**	**Comments**
Austria Austrian Drug Law. Paragraph 10c, Article 3.10	"eine Erklärung, dass die Texte für die Außenverpackung, und gegebenfalls Gebrauchsinformation und Fachinformation außer Firmenspezifischen Angaben sowie Angaben zur Vemeidung von Sinnwidrigkeiten keine textlichen Abweichungen zu der Fachinformation der in Österreich zugelassenenen bzw. registrierten Arzneispezialität aufweise.."	A PI application shall include a confirmation that the labellin texts, pil and SmPC contains the same information as the reference product (RP) in Austria
Germany Annex to the "Hinweise zum Parallelimport von Arzneimitteln", dated 4 August 2004, Version 05, No. 8 of the Annex:	"→ Übernahme der Angaben aus aktueller Gebrauchs- und Fachinformation des Originalanbieters (Bezugszulassung) mit Ausnahme: der Angabe des Pharmazeutischen Unternehmers und Herstellers , der sonstigen Bestandteile, der Packungsgrößen ..., der Haltbarkeitsdauer … ."	- Guidance document on PI available in German only - pil and SmPC for PI should be based upon the RP except for the information regarding the MAH, manufacturer, excipients, pack sizes and shelf life.
Ireland Irish Medicines Board: "Guide to parallel product authorisations for medicinal products for human use", Edition 5, May 2004, page 9	SmPC:"The following particulars should be in accordance with the product authorisation for the Irish-market product: Indications, posology, contra-indications, Precautions and warnings	Only some section are in accordance with the reference product
The Netherlands Homepage der MEB, Parallel import of medicinal producs authorised in the Netherlands", resp. Art. 23, paragraph 10 of the regulation concerning the authorisation of medicinal products	"The package leaflet is identical to that of the reference product with regards to the information under the headings indication, contra-indications, side-effects, dosage, use and route of administration"	
Sweden „The Medical Products Agency´s (MPA) Provisions and Guidelines for Marketing Authorisation of Parallel imported Medicinal Products", (LVFS 2004:8) published 22 April 2004, Guidelines relating to 9§	"The patient information leaflet shall be designed to provide information in accordance with the valid patient information leafet for the direct imported medicinal product [RP], but with presentation of any notable differences"	

Hence, parallel imported products have, by definition, the identical SmPC and pil compared to the originator (reference) product, even in case the authorised texts of the originator differs in the country of importation and exportation. As discussed for generic medicinal products, in an MRP the SmPC and pil would in such a case be harmonised resulting in a 'vertical disharmony'.

On the next two pages, an example is presented, which makes obvious the impact of this provision. Even though the authorised SmPC of the product Neurontin 300 mg capsules (with the active ingredient gabapentine) in the exporting country (the Netherlands) does not have the indication "postherpetic neuralgia" (neuropatische Schmerzen) and can not be used for children under 12 years of age in the exporting country (Netherlands), the texts used by the parallel trader after importation of this product are identical to that of the reference product in Germany (the originator).

In this context, parallel import applications clearly have an advantage. While the regulatory authorites of the CMS in an MRP would classify such a deviation as a "risk to public health", a parallel importer does not even has to justify the different text versions, but automatically receives the texts important for a trouble-free substiution and/or reimbursement.

Table 6	**Parallel-imported product as it is marketed Germany**	**Reference product (originator) in Germany**	**Parallel-imported product as it is marketed in the Netherlands**
Source	BfArM database (www.dimdi.de / AMIS/ öffentlicher Teil): SmPC, dated May 2002 (Neurontin-FI-neu rtf).,	BfArM database (www.dimdi.de / AMIS/ öffentlicher Teil); www.fachinfo.de, SmPC Neurontin, dated June 2005	Medicines data base on the homepage of the Dutch regulatory authority, available at http://www.cbg-meb.nl/uk/prodinfo/index.htm
Product name:	Neurontin 300 mg Kapseln	Neurontin 300 mg Kapseln	Neurontin 300
Licence number:	52431.00.00	47275.01.00	RVG 22482
MAH:	Pharma Westen GmbH	Parke-Davis GmbH	Pfizer BV
Date of grant:	27.08.2001	23.10.2000	10.11.1999
Country of exportation	(1 of 4): The Netherlands, licence no.: RVG 22482	---	---
active ingredient	300 mg gabapentine	300 mg Gabapentin	300 mg gabapentine
Indications	Epilepsie: Monotherapie (einschließlich Erstbehandlung) bei Erwachsenen und Kindern über 12 Jahren mit einfachen und komplexen partiellen Anfällen mit un ohne sekundäre Generalisierung Zusatztherapie bei Erwachsenen und **Kindern ab 3 Jahren** mit partiellen Anfällen mit und ohne sekundäre Generalisierung. **Neuropatische Schmerzen : Zur Behandlung von neuropatischen Schmerzen im Erwachsenenalter**		Neurontin is bestemd als adjuvant-therapie bij patiënten met refractaire partiële epilepsie met of zonder secudaire generaliseerde aanvallen. Neurontin dient aan de bestaande theapie te worden toegevoegd.
Provisions for Children	See above	See above	**Dosering bji kinderen jonger dan twaalf jaar: De werkzaamheid en veiligheid in deze patiëntengroep is nog niet vastgesteld**

Data protection period

As described in section 2.2, an abridged application for a generic medicinal product can not be filed before the expiry of the data protection period. For parallel import applications, however, such a provision is neither included in the Commission Communication on parallel imports, nor in the subsequent case law in front of the ECJ. Even though the wording of the 'old' Article 10 of Directive 2001/83/EC (prior to the amendment by Directive 2004/27/EC),

> *"...(1a) the applicant shall not be required to provide the results of toxicological and pharmacological tests or the resulst of clinical trials, if he can demonstrate:*
> *(iii).. that the medicinal product is essentially similar to medicianl product which has been authorised within the Community .. for not less than [six/ten] years and is marketed in the Member State where the application is made.."*

does not completely rule out the possibility to apply the data protection also in context of parallel import applications, Article 10 (1) of Directive 2004/27/EC has clarified that data protection is only relevant for 'generic medicinal products':

> *"...the applicant shall not be required to provide results of preclinical test and of clinical trials, if he can demonstrate that the medicinal product is a generic of a reference medicinal product..."*

Furthermore, the principle of the simplified procedure for parallel imports is different from the abridged application for generic medicinal products. Rather then 'using' data of an original applicant to complete the application, parallel importer are exempted from having to submit any documentation relating to the medicinal product (results of preclinical tests, clinical trials and pharmaceutical tests), because this data is considered to already be available to the health authorites.

Hence, in the transition period, where different data protection periods (six or ten years) exist between Member States, a generic product approved in a 6-year-country could be imported in parallel in a 10-year-country under the simplified procedure before the data protection period is expired. In case this could be realised for a product which is not protected by any patent or Supplementay Protection Certrificate, the product could be launched a lot earlier that via a MRP under the abridged application.

7 Summary and Future Aspects

With the judgement in the Kohlpharma Case the concept of 'common origin' no longer is a binding requirement for receiving a parallel import authorisation. As a result, the parallel trader needs only to demonstrate, or at least make it plausible, by means of available or accessible information, that the medicinal product to be imported does 'not differ significantly' with regards to safety and efficacy from the medicinal product that is already authorised.

Unfortunately, the ECJ in this case has missed to clarify the degree of similarity necessary in order to take advantage of a simplified procedure and hence automatically reduced the barriers for parallel importation to any product having the same active ingredient as the one already authorised in the country of importation.

Even though up to date, most Member States did not implement the Kohlpharma judgement in their national provisions, at least the Dutch guideline MEB-14-2.0 clearly allows parallel importation even in case the local product and the imported product have a different composition terms of the excipients and do not have a common origin. Hence, it seems possible that also generic medicinal products can be imported in parallel without having to take the route via a mutual recognition procedure.

There are, of course, limitations which would rule out the possibility of such a scenario. However, in case bioavailablity data (showing that the generic parallel import and the originator product are bioequivalent) is available to the authorities or can be provided by a 'neutral' applicant (unrelated to the generic manufacturer) and the parallel imported product has the identical active ingredient (same salt etc.), oral pharmaceutical form and similar appearance (e.g. scorelines) compared to the originator product, a parallel import application for a generic could be successful.

Advantages such as automatically receiving the same indications as the originator product and the possibility of entering the market before the data protection period is expired, are strong arguments to at least try such an application and challenge the ECJ.

Therefore, rather than continuously loosen the requirements for parallel imports under the principle of 'free movement of goods', the rules for generic medinal product should be revisited. For example, why is it necessary for a generic medicinal product already authorised in one Members State to go through a mutual recognition procedure even though the competent authority of the Reference Member State already has in possession all the necessary information for granting a marketing authorisation?

Why is not a risk to public health if a parallel importer markets a product with a SmPC and pil identical to that of the originator product but different to the authorised texts in the country of exportation?

As an aside, according to the information available in the public part of the AMIS database of the BfArM, the parallel import authorisation for Jumex with reference to the marketing authorisation for Movergan (the products involved in the Kohlpharma Case) has not yet been granted. Maybe, the next court case in front of the ECJ is already on its way !?

Let´s hope more clarification is provided in the future. In the meanwhile, the appeal to generic manufacturers is:

Get in while you can!

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

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