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The Scope of Global Marketing Authorisations within the EU Legal Framework of Regulatory Data Protection for Reference Medicinal Products

I. Background of Regulatory Data Protection

Regulatory Data Protection (“RDP”) shelters research and development investments carried out by pharmaceutical companies, at a point where the term of a patent might be exceeded. During the RDP term the data generated as investment results of pre-clinical tests and of clinical trials of a medicinal product may not be referred to by generic competitors.

Thus, it completes the patent protection and provides another incentive for further investments into the improvement and development of innovative medicinal products.

On the other side generics do not merely facilitate, but induce competition and, thereby, relieve national health-care systems of costs for medicinal products. Furthermore, references to existing data originating from pre-clinical tests and clinical trials prevent unnecessary testing on humans and animals.¹ In the end, it is up to the discretion of the legislator to strike a balance between investment protection and public interest, after a certain period of time.

The European legislator has balanced these interests in Article 10(1) of Directive 2001/83:²

“[...] the applicant shall not be required to provide the results of pre-clinical tests and of clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 6 for not less than eight years in a Member State or in the Community. A generic medicinal product authorised pursuant to this provision shall not be placed on the market until ten years have elapsed from the initial authorisation of the reference product”

and in Article 14(11) of Regulation 726/2004:³

“Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance

with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies”.

In 2004 the Global Marketing Authorisation (GMA)⁴ was implemented into the EU regulatory framework of RDP.⁵ The concept of GMA subsumes various authorised developments of one medicinal product under one and the same GMA. Since the RDP is merely granted once per GMA, the latter defines and restricts the scope of RDP. Therefore, the concept of GMA must be construed within the Regulations’ wording according to the object and purpose (“*effet utile*”) of RDP while likewise balancing between the conflicting interests, i.e. investment protection and public interests.

Above all, the national healthcare systems relieve of costs for (competitive) medicinal products, nevertheless, despite the pressure from public interests, the concept of GMA remains prone to restrictive interpretations of the scope of RDP, which is still rather unclear in regard to certain developments, namely those which are of a significant innovative nature, but may also be authorised as a variation. While the ECJ had dealt with equivalent issues in *Novartis*⁶ under the “old legislation” before the concept of GMA was implemented, a pending case at the General Court⁷ awaits a close assessment of the “new” regulatory framework focussing on the issue whether or not also substantially innovative developments in the sense of Article 3(2) of Regulation 726/2004 are part of the same GMA and, thereby, its inherent restrictive effects on RDP.

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1 Recital 10 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67.

2 OJ L 311, 28.11.2001, p. 67.

3 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for

the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1.

4 Article 6(1) of Directive 2001/83.

5 Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, OJ L 136, 30.4.2004, p. 34.

6 ECR 2004 I-04403, Case C-106/01.

7 Case T-67/13, action brought on 1 February 2013 – Novartis Europharm v Commission, OJ 2013/C 101/53.

The following paper will demonstrate that the innovative nature of a medicinal product or development is the decisive factor under the “new” (post *Novartis* case) RDP framework as ultimately shown by the fact that certain alterations which reached the “innovation hurdle” are entitled to apply for a new marketing authorisation (“MA”) under a new name, hence, be treated as a new medicinal product.

II. Wording of Article 6(1) of Directive 2001/83

Article 6(1) of Directive 2001/83 implements the GMA into the regulatory framework:

“[...] When a medicinal product has been granted an initial marketing authorisation in accordance with the first subparagraph, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 10(1) [...]”

Article 6(1) of Directive 2001/83 applies to centrally authorised, as well as nationally authorised medicinal products as the first sentence of Article 6(1) refers to authorisations granted under Directive 2001/83 and to authorisations granted under Regulation 726/2004.

According to the wording (the primary foundation of any legal interpretation⁸) of Article 6(1) of Directive 2001/83, merely those developments of a medicinal product which are enumerated in the provision fall within the scope of the GMA (“additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions”). Still, in particular, the notions *variations* and *extensions* remain rather ambiguous under the sheer wording.

III. Systematic Interpretation

Regulations and Directives, such as Directive 2001/83, are subject to systematic interpretation⁹ and to be interpreted in the regulatory context.

1. Variation Regulations

Therefore, variations and extensions in the sense of Article 6(1) of Directive 2001/83 are to be defined according to the “Variation Regulations” (currently Regulation 1234/2008¹⁰ and before Regulations 1084/2003 and 1085/2003¹¹), read in conjunction with Directive 2001/83.

2. Background of Article 6(1) of Directive 2001/83 (GMA)

The “Variation Regulations” distinguish between changes to an authorised medicinal product that can be assessed and authorised through an accelerated procedure, called variations, and changes which are considered to be so fundamental that they have to be assessed and authorised through a full new assessment procedure, called extensions. At the time of the introduction of the GMA in the law, the addition of a new strength, new pharmaceutical form, new administration route and new presentation, was classified as an extension leading to a complete new assessment and a new MA. However, the Variations Regulations applicable at that time (Regulation 1084/2003 and Regulation 1085/2003) explicitly stated that the name for the extension authorisation was the same as for the marketing authorisation for the existing medicinal product. Hence, extensions, even though authorised through separate marketing authorisations, were not considered to be new medicinal products. This is reflected in the wording of Article 6(1) of Directive 2001/83. The legislator kept this regulatory framework in mind when implementing the GMA in 2004 and chose the wording of Article 6(1) of Directive 2001/83 accordingly, in order to clarify the scope of the GMA.¹²

According to Article 6(1) it is not of relevance whether the extension or variation was authorised separately under the same name or by amendment of the initial MA. Therefore, all medicinal products authorised as variations or extensions are considered to fall within the same GMA.

8 *Lutter*, JZ 1992, 593, 599; settled case-law of the ECJ, Case 38/69, ECR 1970, 47, 57 f. (12/13); Case 6/77, ECR 1977, 1291, 1298 f., (8/12); Case 139/77, ECR 1978, 1317, 1332, (11); Case 260/78, ECR 1979, 2693, 2701, (5); Case 44/79, ECR 1979, 3727, 3743 f., (11); Case 118/79, ECR 1980, 1183, 1190, (5); Case 107/84, ECR 1985, 2655, 2666 f., (10 f.).

9 ECJ, Case 6/64, ECR 1964, 1251, 1270; Case 6/72, ECR 1973, 215, 244, (22); Case 111/76, ECR 1977, 901, 910, (17/18); Case 30/77, ECR 1977, 1999, 2010, (13/14); Case 283/81, ECR 1982, 3415, 3430, (20); Case 31/87, ECR 1988, 4635, 4656, (15); Case C-36/98, ECR 2001, I-779, 827, (49); *Lutter*, JZ 1992, 593, 602.

10 Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7–24.

11 Commission Regulation (EC) No 1085/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93, OJ L 159, 27.06.2003, p. 24–45.

12 Directive 2004/27/EC of the Parliament and of the Council of 31 March 2004, OJ L 136, 30.04.2004, p. 34.

IV. Teleological Interpretation

Considering the object and purpose¹³ of the GMA, which must be construed according to the *effet utile* of RDP while likewise balancing between the conflicting interests, the question remains whether Article 6(1) of Directive 2001/83 (GMA) also captures “developments” which fall within the scope of Article 3(2) of Regulation 726/2004 or merely developments in the sense of the Variation Regulations which were authorised accordingly. The first being developments which, because they fulfil the innovation specific criteria of Article 3(2) of Regulation 726/2004, are entitled to a separate MA under a different name, similar to a new medicinal product.

1. Object and Purpose of GMA and RDP

The object of the GMA is to capture all variations of *one and the same* medicinal product. The underlying reasoning is to enable generic competitors to refer to the complete data package of one medicinal product (also cross-reference) and the other is to limit the RDP.¹⁴ The purpose of the GMA would be best served through extensive interpretation of Article 6(1) of Directive 2001/83.

Whereas the object and purpose of the RDP indicate a restrictive interpretation of the scope of the GMA. Object and purpose of RDP are directed to protect investments carried out by pharmaceutical companies and to provide an incentive for investments into further innovative research on developments (including improvements) of innovative medicinal products and their new therapeutic indications. The more substantial improvements of the original product fall within the scope of the GMA, the less investments are protected by RDP. As a consequence, the scope of the GMA limits the RDP and bears the risk of contradicting the RDP if interpreted too broadly.¹⁵

The legislator has struck this balance in Article 3(2) of Regulation 726/2004:

“Any medicinal product not appearing in the Annex may be granted a marketing authorisation by the Community in accordance with the provisions of this Regulation, if:

- (a) the medicinal product contains a new active substance which, on the date of entry into force of this Regulation, was not authorised in the Community; or*
- (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or techni-*

cal innovation or that the granting of authorisation in accordance with this Regulation is in the interests of patients or animal health at Community level”.

Before Part B of Annex of Regulation 2309/93 provided that option:

“Medicinal products developed by other biotechnological processes which, in the opinion of the Agency, constitute a significant innovation. Medicinal products administered by means of new delivery systems which, in the opinion of the Agency, constitute a significant innovation”.

In general, solely new medicinal products enjoy RDP and their developments do not trigger a separate protection term. However, as the following discussion will show, innovative developments in the sense of Article 3(2) of Regulation 726/2004, which surpass the “innovation hurdle” of Article 3(2) and are authorised as new medicinal products in accordance with explicit criteria and procedures laid down in the law, enjoy RDP, because in substance they are equivalent to new medicinal products, hence, the new MA with a new name. By that the legislator determined which developments/investments deserve to be considered different from already registered medicinal products on the European market (innovative and new) and therefore attract RDP.

2. Innovation Inherent Criterion

The innovation criterion is inherently anchored in the object and purpose of the RDP. As already stated, RDP is granted to protect investments and to give an incentive for further investments. In that logic protection shall only benefit those who substantially invest into innovative medicinal research to an extent comparable to research of a new medicinal product containing a new active substance.

3. Article 3(2) of Regulation 726/2004 versus Variation

In principle, developments that reach the “innovation hurdle” set out in Article 3(2) of Regulation 726/2004 are authorised by a separate MA with a new name.

Still, in many cases these developments may also be authorised as variations under the same name and would, if authorised as variations, fall within the scope of the GMA. By contrast, the procedure of Article 3(2) of Regulation 726/2004 may be for example chosen for safety reasons in order to avoid confusion about e.g. the dosage or other product characteristics.

Nevertheless, developments of medicinal products in the sense of Article 3(2) of Regulation 726/2004 and Part B of Annex of Regulation 2309/93 are not simple variations

¹³ ECJ, Case 25/70, ECR 1970, 1161, 1174, (16); Case 35/71, ECR 1971, 1083, 1093, (3); Case 67/74, ECR 1975, 297, 306, (5); Case 6/77, ECR 1977, 1291, 1298 f., (8/12); Case 126/78, ECR 1979, 2041, 2052, (10 f.); Case 77/79, ECR 1980, 247, 258 f., (6); Case 152/79, ECR 1980, 1495, 1507, (12); Case C-36/98, ECR 2001, I-779, 827, (49); *Bleckmann*, NJW 1982, 1177, 1178; *Lutter*, JZ 1992, 593, 602.

¹⁴ As shown in the Novartis ruling: ECR 2004 I-04403, Case C-106/01.

¹⁵ Also ECJ, Opinion of Advocate General Jacobs delivered on 23 January 2003, Case C-106/01, at point 55.

of a medicinal product, even though they would also fulfil the requirements of variations. In the regulatory context they are considered “a significant [...] innovation”¹⁶ and therefore constitute a new medicinal product, regardless the “known” active substance.

4. Article 3(2), More Than A Variation

One might raise the counterargument that the so called optional scope merely provides a special regime for substantial variations, and does not lead to a classification as a new medicinal product as indicated by the new MA and name. This interpretation would fall short to the regulatory system.

First of all, variations are not referred to in Article 3(2) of Regulation 726/2004.

Secondly, the rationale of the Variation Regulations is not applicable to the regulatory framework of the RDP. The current Variation Regulation, which categorises variations in minor (Annex I) and major (Annex II) variations, is to be seen in light of the objective to safeguard the public health according to the risk that might be induced by the alteration.¹⁷ Opposed to that, Article 3(2) of Regulation 726/2004 grants innovative products access to the centralised procedure, without any reference to the variation procedure. Medicinal products authorised under Article 3(2) of Regulation 726/2004 are distinct, not merely due to the procedure, but due to the medicinal product at issue which fulfils the innovation specific criteria laid down in this provision (which is to be controlled by the EMA) having regard to the fact that the applicant chooses to invest into the required data and applies for an authorisation which acknowledges the innovative and new nature of the development, i.e. under the Article 3(2) procedure opened to the applicant for that purpose.¹⁸

Therefore, the hypothesis that an innovative medicinal product could have been authorised as a variation, however, was in fact authorised under Article 3(2) of Regulation 726/2004, does not make it a variation in the regulatory context and, thus, bears no consequence for the regulatory framework of RDP. Even though these developments could have been authorised as variations, once the track of an Article 3(2) procedure has been chosen and the applicant risks being denied by the EMA and the resulting delay in authorisation, the distinctive path of an authorisation for an original product has been taken, and therefore the variation option is to be disregarded.

Also from a historical perspective two aspects need to be differentiated.

The ECJ clearly stated that the scope of data that may be referred to for assessing the safety and efficacy is one thing, and the scope of the RDP another:

“Accordingly, and pursuant to the first subparagraph of Article 5 of Directive 65/65, as amended, an application for marketing authorisation must be refused, inter alia, where, on the basis of data in the possession of the com-

*petent authority, it appears that a medicinal product is harmful or lacks efficacy. Clearly that authority is not precluded from basing its refusal on data submitted by other applicants, even if that data is protected within the meaning of Article 4.8(a)(iii) of Directive 65/65, as amended.”*¹⁹

Conclusions drawn from safety and efficacy considerations are not directly transferable to the assessment of the RDP.

Advocate General Jacobs had a similar approach when stating:

*“However, it is in my opinion untenable to assert, as the first approach does, that, as a consequence of the freedom to refer to all data in verifying safety and efficacy, a competent authority cannot also perform a separate and independent assessment of an application in order to verify the adequacy of the documents and particulars submitted in support of that application. Such an approach would remove any element of data protection from the authorisation procedure and is therefore contrary to point 8(a)(iii).”*²⁰

As already stated, the RDP balances the protection of investments carried out by pharmaceutical companies and the public interest in generic medicinal products.²¹ Thus, not the similarity to variations is relevant but whether the alteration is innovative in the eyes of the legislator and therefore deserves separate RDP. The ECJ has clearly stated, that it is up to the legislator to “reinforce the rules for the protection of innovating undertakings”.²² The legislator has done so, by allowing certain alterations which reached the “innovation hurdle”, to be granted a new MA under a new name and be treated as a new medicinal product. Furthermore, Article 6(1) of Directive 2001/83 does not intend to contradict Article 3(2) of Regulation 726/2004 by subsuming Article 3(2) MAs under the GMA.

16 Article 3(2) of Regulation 726/2004: “a significant [...] innovation” or Before Part B of Annex of Directive 2001/83: “[...] Medicinal products [...] which, in the opinion of the Agency, constitute a significant innovation.”

17 Recital 3 und 4 Regulation 1234/2008.

18 As opposed to Advocate General Jacobs in his Opinion delivered on 23 January 2003, ECJ – Case C-106/01, at point 57: “To exclude the application of the Generics decision whenever a subsequently authorised variant of a reference product had been given a new designation would elevate form over substance, and would create an easy route for applicants to gain additional data protection in circumvention of Generics”.

19 ECR 2004 I-04403, Case C-106/01, at point 31.

20 Also ECJ, Opinion of Advocate General Jacobs delivered on 23 January 2003, Case C-106/01, at point 55.

21 Recital 10 of Directive 2001/83.

22 ECR 2004 I-04403, Case C-106/01, at point 28; ECR 1998 I-07967, Case C-368/96, at point 52.

5. Innovation Criteria in Article 14(11) of Regulation 726/2004

One may argue that Article 14(11) of Regulation 726/2004 provides a conclusive regulation of RDP for innovative products and aims at the scope of Article 3(2) of Regulation 726/2004:

“[...] in which connection the latter period shall be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies.”

If that was the case, why does Article 14(11) of Regulation 726/2004 not simply refer to Article 3(2)? Moreover, these two tracks need to be differentiated since the applicant needs to undertake different developments for a different dossier than for an authorisation under Article 3(2) of Regulation 726/2004.

V. Coherency under the Rule of Law

Another crucial point of any (EU or national) regulation is coherency as a general principle under the rule of law and proportionality, requiring that the regulatory “*objective is being pursued in a consistent and systematic manner*”²³. Any interpretation under the rule of law has to create results which are consistent with the regulatory framework and its systematic approach.

Finally, it would be inconsistent to deny the same marketing authorisation holder RDP, though to grant RDP in the hypothetical case of a third applicant submitting the same medicinal product.

How can it make a difference whether a hypothetical third person or the initial marketing authorisation holder reaches the innovation hurdle and registers the same active substance in another pharmaceutical form, strengths and indication? The legislation bares no indication for such differentiation and uncertainty.

Furthermore, in *Novartis* the ECJ held, that the principle of non-discrimination also applies to pharmaceutical regulation:

*“According to settled case-law, the principle of non-discrimination requires that comparable situations not be treated differently and different situations not be treated in the same way unless such treatment is objectively justified (see, inter alia, Case 106/83 Sermide [1984] ECR 4209, paragraph 28, and Case C-137/00 Milk Marque and National Farmers’ Union [2003] ECR I-7975, paragraph 126).”*²⁴

In light of that ruling it is safe to say, that the ECJ would hold the situation of an Article 3(2) applicant comparable to a third applicant. In *Novartis* the ECJ rejected the comparison because the initial marketing authorisation holder applies for a new medicinal product providing the necessary data to prove its safety and efficacy, whereas the generic competitor has to prove the similarity to the originator product:

*“The situation of the applicant for marketing authorisation for product B is, in any event, not comparable to that of the applicant for marketing authorisation for product C. When the latter applicant applies for marketing authorisation, product B is authorised and the authorities are assured of the safety and efficacy of that product.”*²⁵

Here, we would have two applicants of a new product, who are comparably applying for an authorisation. A different treatment would objectively not be justified.

VI. Previous Regulation

Due to the structure and categories of the current regulation, the “innovation hurdle” has become a decisive factor. The current variation regulation is, as opposed to the regulatory context at the time of the *Novartis*²⁶ ruling, clearer about which developments are considered variations and whether the market authorisation holder has to apply for an amendment of the initial MA or apply for a new MA under the original name or a new MA under a new name.

In principle, all changes in strength, pharmaceutical form or route of administration (which in fact are all extensions) and all other variations and extensions of the initial product do no longer lead to a separate marketing authorisation for a medicinal product with a new name. Instead, those authorisations lead to an amendment of the terms of an existing marketing authorisation or a separate MA under the existing name. Merely in special situations and according to special procedures laid down in Article 3(2) of Regulation 726/2004, the marketing authorisation holder is entitled to apply for a new and independent authorisation, not leading to the amendment of the terms of an existing authorisation. Since these procedures are controlled by the authorities on the basis of very specific criteria (e.g. innovative products, orphan drugs, medicinal products of paediatric use)²⁷, the current legislator obviously considers the latter a substantial qualification for a new and independent authorisation.

23 ECR 2010 I-08149, Case C-46/08 – Carmen Media Group, at point 53.

24 ECR 2004 I-04403, Case C-106/01, at point 69.

25 ECR 2004 I-04403, Case C-106/01, at point 70.

26 ECR 2004 I-04403, Case C-106/01.

27 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1; Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on products for paediatric use and amending Regulation (EEC) No 1768/92, Directives 2001/20/EC and 2001/83/EC, and Regulation (EC) No 726/2004.

If the optional clause did not lead to a new MA and RDP, the rationale of Article 3(2) Regulation 726/2004 would merely be to grant a market authorisation holder a new name. Certainly, a new name is of interest for pharmaceutical companies. However, the reasoning behind the so called optional clause of Article 3(2) is not merely to grant access to the centralised procedure, but also to increase investments into medicinal research and their placement on the European market by providing an incentive in form of RDP for further investments into the improvement and development of innovative medicinal products and their new therapeutic indications. Otherwise, data, generated from investments into innovative medicinal products, would not be protected by RDP and the medicinal product would merely be marketed under a new name, regardless its innovative nature.

In light of the similar regulatory rationale underlying the authorisation of innovative products and the authorisation of orphan drugs and medicinal products for paediatric use, this reasoning becomes evident:²⁸ The legislator intended to give an incentive to develop products for unmet medical needs and not take it away.

VII. The Cases Novartis and Generics under Previous Legislation

The innovation criteria is also no surprise in light of the previous rulings of the ECJ. Even though these rulings are not applicable to the current regulation, because the legislator turned away from the “essential similarity criterion” (essential similarity has not been implemented into the new regulatory framework, as demonstrated by the wording of Article 14(11) of Regulation 726/2004, Article 6(1) and 10(1) of Directive 2001/83). However, these rulings remain interesting regarding the innovation criterion.

The ECJ addressed the issue of innovation in *Novartis*²⁹, which applied the predecessor regulation.

To illustrate that argument, the previous case-law shall be presented:

1. Novartis, Generics and Innovation

Before, Article 4(8) of Directive 65/65/EEC³⁰ provided RDP:

*“[...] The applicant shall not be required to provide the results of pharmacological and toxicological tests or the results of clinical trials if he can demonstrate:
[...] or that the medicinal product is essentially similar to a product which has been authorized within the Community[...].”*

Under previous law, the safety and efficacy of the generic product and the scope of the RDP was defined by the essential similarity between the originator product and the developed product.

In his opinion delivered to the *Novartis* case, Advocate General Jacobs proposed the active substance as the decisive factor to determine essential similarity:

“It best succeeds in balancing the conflicting objectives of data protection and the avoidance of unnecessary testing on humans and animals by reserving additional data protection for the most significant modifications to an original product, namely those which involve the introduction of a new active substance.”³¹

This proposal was also based on the intention to avoid legal uncertainty.³²

The ECJ, on the other hand, stressed that all three criteria have to be considered in *Generics*³³ and confirmed that ruling in *Novartis*.³⁴

“Having regard to the foregoing, the answer to the first part of the first question must be that Article 4.8(a)(iii) of Directive 65/65, as amended, is to be interpreted as meaning that a medicinal product is essentially similar to an original medicinal product where it satisfies the criteria of having the same qualitative and quantitative composition in terms of active principles, of having the same pharmaceutical form and of being bioequivalent, unless it is apparent in the light of scientific knowledge that it differs significantly from the original product as regards safety or efficacy.

As regards the second part of the first question, it follows from the foregoing considerations that the competent authority of a Member State may not disregard the three criteria set out above when it is required to determine whether a particular medicinal product is essentially similar to an original medicinal product.”³⁵

In that context, the European Commission attempted to submit the innovative nature of a development as a decisive factor for the scope of the RDP:

“The Commission submits that, having regard to the fact that the general purpose of the provision at issue is to ensure fair protection for innovation, it should be possi-

28 Supra footnote 28. The regulatory framework provides specific exemptions which allow applicants to apply for a separate MA under a new name for a medicinal products containing the same active substance as a previously authorised product: Orphan drugs, paediatric use (PUMA) and Article 3(2) of Regulation 726/2004.

29 ECR 2004 I-04403, Case C-106/01, at point 28.

30 Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, OJ L 22, 9.2.1965, p. 369–373.

31 ECJ, Opinion of Advocate General Jacobs delivered on 23 January 2003, Case C-106/01, at point 61.

32 ECJ, Opinion of Advocate General Jacobs delivered on 23 January 2003, Case C-106/01, at point 59.

33 ECR 1998 I-07967, Case C-368/96.

34 ECR 2004 I-04403, Case C-106/01, at point 28.

35 ECR 1998 I-07967, Case C-368/96, at point 37.

*ble in the exceptional circumstances of major therapeutic innovation – essentially where there is an entirely new therapeutic indication – to protect the results of new pharmacological and toxicological tests and clinical trials relating to the reference product in their turn in the same way as for any new medicinal product.*³⁶

The Court addressed that argument stating:

*“Furthermore, the diverse nature of the criteria proposed by the Commission in order to determine which therapeutic indications constitute a major therapeutic innovation means that the concept of ‘major therapeutic innovation’ is insufficiently precise. In the circumstances, application of those criteria would in any event tend to undermine the principle of legal certainty.”*³⁷

Thus, innovation was discussed, already under the previous law, as an exemption from the rule. The legislator decided to follow that approach by elevating the innovation hurdle to a decisive factor for full RDP. As shown above, the regulation now emphasises the innovative nature of developments. Developments which are not significant in comparison to the originator product, have to be authorised as a variation or extension to the initial MA and are captured by the GMA, those which are significantly innovative and are authorised under a new MA as a new medicinal product with a new name and are not captured by the GMA.

Legal certainty was the reason, why the Court disregarded the innovation argument in the *Novartis*³⁸ ruling. The previous regulation did not provide for a sufficient legal basis to determine innovation as the decisive factor. Instead, the ECJ referred *de lege ferenda* to the legislator to “reinforce rules for the protection of innovating undertakings”.³⁹ Indeed, the legislator then followed the ECJ’s proposal. By contrast to the previous regulation applied in the *Novartis* ruling, the current regulation remedies the Court’s concerns by expressly providing for a strong systematic regulatory interaction between the optional clause of Article 3(2) (read together with Article 14(11)) of Regulation 726/2004 on the one side and Article 6(1) (read

together with Article 10(1)) of Directive 2001/83 on the other side, thereby strengthening innovation as the decisive factor. According to special procedures supervising the criteria laid down in Article 3(2) of Regulation 726/2004, EU law considers specifically innovative products, orphan drugs and medicinal products of paediatric use⁴⁰ (and, respectively, their substantially new therapeutic indications) as qualifying for a new and independent authorisation. Hence, the General Court and the ECJ have currently every reason to confirm innovation as the decisive factor.

2. Same Active Substance

By contrast to Advocate General Jacobs’ approach under the previous regulation in *Novartis*⁴¹, under the current regulatory framework and its regulatory interaction between the optional clause of Article 3(2) of Regulation 726/2004 and the concept of GMA (construed according to the *effet utile* of RDP) under Article 6(1) of Directive 2001/83, the active substance must not be considered a requirement overruling innovation as the decisive factor. Instead, the active substance may merely be qualified as an indicator among others, but is not alone the decisive factor for innovation.⁴² Otherwise, the legislator would have implemented the active substance in the wording of consolidated Article 6(1) of Directive 2001/83, considering how simple such an implementation would have been. In light of legal certainty, it seems arbitrary to assume the active substance to be the legislator’s intend under the current regulatory framework.

One may not argue that, without the active substance as the decisive factor, the RDP might be prolonged repeatedly. If a development of a medicinal product, containing the same active substance, did not surpass the innovation hurdle, a stand-alone MA under a new name would not be granted to the applicant. Due to the innovation hurdle under the optional clause of Article 3(2) of Regulation 726/2004 there is no significant risk for repetition or doubling of MAs. Allowing that argument would also mean to reduce a medicinal product to its active substance, which has no bearing in the regulation and would ignore that an applicant does not solely register an active substance.

VIII. Innovation of Medicinal Products under the Rule of Legal Certainty

To apply the concept of “essential similarity” with reference to the *Generics*⁴³ and *Novartis*⁴⁴ rulings to medicinal products registered under a separate MA under a new name would raise the issue of legal certainty under Article 6(1) of Directive 2001/83. As demonstrated, the concept of “essential similarity” has no basis in the new regulation and is therefore arbitrary. *Generics* and *Novartis* might have set the beginnings of the GMA concept, however, the

36 ECR 1998 I-07967, Case C-368/96, at point 45.

37 ECR 1998 I-07967, Case C-368/96, at point 48.

38 ECR 2004 I-04403, Case C-106/01.

39 ECR 2004 I-04403, Case C-106/01, at point 52; ECR 1998 I-07967, Case C-368/96, at point 28.

40 OJ L 18, 22.1.2000, p. 1; Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on products for paediatric use and amending Regulation (EEC) No 1768/92, Directives 2001/20/EC and 2001/83/EC, and Regulation (EC) No 726/2004.

41 ECJ, Opinion of Advocate General Jacobs delivered on 23 January 2003, Case C-106/01, at point 61.

42 As also shown by the full RDP term granted to combination products which consist of already centrally authorised active substance.

43 ECR 1998 I-07967, Case C-368/96.

44 ECR 2004 I-04403, Case C-106/01.

legislator deliberately chose a modified approach. Defining the scope of the RDP as to whether the medicinal product contains the same active substance or is essentially similar to another product would go so far as to disregard the regulatory interaction in force between the optional clause of Article 3(2) of Regulation 726/2004 and the concept of GMA (construed according to the *effet utile* of RDP) under Article 6(1) of Directive 2001/83. In addition, with that interpretation, lacking any justification, investments into research and development of medicinal products would be burdened with additional risks, reducing the incentive to innovate also therapeutic indications. That interpretation would contradict the *effet utile* of RDP. Paradoxically, it would give a counterfactual incentive to perform repetitive tests on humans and animals in a permanent search for new active substances to create grounds for the acknowledgment of the medicinal product as a new medicinal product, instead of providing an incentive to innovate “known” substances. Such a counterfactual incentive approach would erode the purpose of the legislator to enhance innovation of medicinal products under the rule of legal certainty.⁴⁵

IX. Conclusions

Having regard to the regulatory interaction between the optional clause of Article 3(2) of Regulation 726/2004 and Article 6(1) of Directive 2001/83, EU law considers specifically innovative products, orphan drugs and medicinal products of paediatric use as qualifying for a new independent authorisation and for a new RDP, thus, strengthening innovation as the decisive factor.

Article 3(2) of Regulation 726/2004 establishes special procedures supervising the innovation criteria, thereby avoiding that RDP might be prolonged repeatedly.

As a result the MAs of these innovations, qualifying under the special procedures of Article 3(2) of Regulation 726/2004, are not part of the GMA of the original medicinal product under Article 6(1) of Directive 2001/83.

The proposed understanding of Article 6(1) of Directive 2001/83 also benefits transparency. This way, the market authorisation holder, as well as the generic competitor, will know at any point – upon completion of the qualifying procedures under Article 3(2) of Regulation 726/2004 – whether RDP is in effect.