

EU REGULATORY DATA PROTECTION FOR LIFE SCIENCES COMPANIES

This document is published by Practical Law and can be found at: uk.practicallaw.com/w-009-9967
Get more information on Practical Law and request a free trial at: www.practicallaw.com

This note discusses regulatory data protection (or data exclusivity) and market protection (marketing exclusivity). It identifies their legal bases, defines relevant legal terms and case law, and explains why these forms of protection are essential for the innovative medicines industry. This note also discusses the periods of time for which these forms of protection exist and how they interrelate with protection afforded by patents and supplementary protection certificates. Additionally, this note summarises enforcement issues, including possible challenges to the grant (or refusal to grant) of generic marketing authorisations.

by *Marjan Noor* and *Rafi Allos, Allen & Overy*

CONTENTS

- Scope of this note
 - Full or stand-alone applications
- Legislative sources and guidance
 - “Full-mixed” applications
- What is regulatory data protection?
 - Abridged applications
- Regulatory data protection and market protection period
 - Significant clinical benefit
 - Fixed combination (Article 10b of Directive 2001/83/EC)
 - Medicinal products protected under previous rules
 - Informed consent (Article 10c of Directive 2001/83/EC)
- Definition of reference medicinal product?
 - Generic and hybrid medicinal products
- Global marketing authorisation
 - Same marketing authorisation holder
 - New vs same active substance
- Particulars to accompany an application for a marketing authorisation
 - Other regulatory data protection periods
 - New therapeutic indication for well-established substance
 - Change of classification (prescription-only medicine to OTC)
 - Enforcement and standing to challenge grant of generic marketing authorisation

RESOURCE INFORMATION

RESOURCE ID

w-009-9967

RESOURCE TYPE

Practice note

CREATED ON

3 May 2018

JURISDICTION

United Kingdom

European Union

SCOPE OF THIS NOTE

An applicant for marketing authorisation of a generic, hybrid or biosimilar medicine (see *Abridged applications*) is not required to provide its own generated full data package if the innovator medicine’s regulatory data protection (RDP) period has expired. The grant of RDP (and marketing protection) therefore aims to strike a balance between rewarding costly and extensive research and innovation on the one hand and avoiding the unnecessary repetition of tests on humans and animals on the other. This note explains when regulatory data and marketing protection is granted, the specific circumstances under which marketing protection may be extended, and how innovative medicines developers seek to protect their products through the combined use of regulatory data and marketing protection, patents and supplementary protection certificates (SPCs).

The regulatory framework concerning paediatric and orphan medicinal products is excluded from the scope of this note.



LEGISLATIVE SOURCES AND GUIDANCE

EU law governing the regulation of medicinal products for human use is contained chiefly in the following legislation:

- [Directive 2001/83/EC](#) on the Community code relating to medicinal products for human use.
- [Regulation \(EC\) No 726/2004](#) laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA).

There are also several EU regulatory guidelines relevant to RDP, most notably:

- The European Commission's (EC) "Notice to Applicants, Volume 2 of the Rules Governing Medicinal Products in the European Union", and in particular, "Volume 2A, Chapter 1 – Marketing Authorisation" (EC's Notice to Applicants (Volume 2A, Chapter 1)) (see [EC: EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use](#)).
- Guidance on generic and hybrid applications and on biosimilars published by the EMA (see [EMA: Generic and hybrid applications](#) and [Biosimilar medicines: marketing authorisation](#)).
- Guidance on generic applications published by the Heads of Medicines Agencies (see [CMDh: Q&A - Generic Applications](#) and [Generics in \[Mutual Recognition Procedure\] and \[Decentralised Procedure\]](#)).
- A further legislative source relating to the protection of pharmaceutical regulatory data that is relevant in the EU is the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) (although EU law provided for the protection of pharmaceutical regulatory data before TRIPS was signed). As members of the World Trade Organization, the EU and its 28 member states are bound by TRIPS. Article 39.3 of TRIPS provides for the protection of pharmaceutical regulatory data as follows:

"Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."

The position of the EU is that the most effective way to fulfil the obligation in Article 39.3 of TRIPS to protect test data against unfair commercial use is to provide for data exclusivity over a reasonable period of time by denying the regulatory authorities the possibility of relying on such data for that period of time (see [EC: Legal Issues related to Compulsory Licensing under the TRIPS Agreement](#)).

WHAT IS REGULATORY DATA PROTECTION?

To avoid unnecessary repetition of pre-clinical tests and clinical trials, EU regulatory law defines certain abridged procedures for obtaining a marketing authorisation in which an applicant does not need to provide all of the data that is required as part of a full marketing authorisation application. Instead, the applicant can rely on the data submitted in relation to a previously authorised medicinal product which is termed a "reference medicinal product" in the legislation (see [Abridged applications](#)).

RDP, also referred to as regulatory data exclusivity, is a form of protection for the data package that is submitted to support a marketing authorisation application for an innovative medicinal product in the EU. It is distinct from, and can run in parallel with, intellectual property protection for research and development (R&D) and innovation such as patents and trade secrets.

REGULATORY DATA PROTECTION AND MARKET PROTECTION PERIOD

Article 10(1) of [Directive 2001/83/EC](#) states:

"By way of derogation from Article 8(3)(i) ... 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 ...”

Accordingly, Article 10(1) (commonly known as the “generic route”) allows an applicant to rely on the reference medicinal product’s data only after the expiration of the RDP period, which lasts for eight years from the date of first authorisation in the EU. After the expiry of the RDP period, the regulatory authority can satisfy itself of the safety and efficacy of the later product on the basis of the reference medicinal product’s data package. Thereafter, the generic product cannot be placed on the market for a further two years, even if authorised, as a result of marketing protection that is granted to the reference medicinal product. This combined ten-year period can be extended by an additional one year of marketing protection if the reference product is authorised for a new indication which brings a significant clinical benefit in comparison with existing therapies (see *Significant clinical benefit*). The period of RDP and marketing protection under the current EU regime is commonly referred to as the “8+2(+1)” approach.

The same periods of protection are applicable to medicinal products that are referenced in hybrid and biosimilar applications and medicinal products authorised through the centralised procedure (*Article 14(11), Regulation (EC) 726/2004*).

Significant clinical benefit

Article 10(1) of *Directive 2001/83/EC* and Article 14(11) of *Regulation (EC) 726/2004* state that the “8+2” year period can be extended by an additional year of marketing protection:

“to a maximum of eleven 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”.

Guidance on what constitutes a significant clinical benefit has been published by the EC and is available on its website, and the competent authority reviewing an application for a new indication will determine if it brings a significant clinical benefit in accordance with this guidance.

The additional year of marketing protection applies to all indications of the reference medicinal product such that a generic cannot be placed on the market for any indication and irrespective of whether it is authorised for the new indication that brings significant clinical benefit. As the overall period of protection cannot extend beyond 11 years in respect of a particular reference medicinal product, the additional year of marketing protection can only be obtained once. The EC’s guidance is that one should have regard to the “global marketing authorisation” concept defined in Article 6(1) of *Directive 2001/83/EC* in determining whether a product has already benefited from the additional year of protection. The consequence of this is that if an authorisation for a new indication has resulted in a one-year extension of marketing protection for a product, any further authorisations that belong to the same global marketing authorisation cannot benefit from a further extension of marketing protection. For example, the same marketing authorisation holder is granted authorisations for Products A and B which are different pharmaceutical forms of the same active substance and therefore belong to the same global marketing authorisation. If Product A is authorised for a new indication which results in the one-year extension of marketing protection, it is not possible to obtain a further one-year extension of marketing protection as a result of Product B being separately authorised for a further indication that brings significant clinical benefit. However, the one-year extension of marketing protection granted as a result of the new indication for Product A will apply to both Products A and B (see *Global Marketing Authorisation* and section 6.2 of the *EC’s Notice to Applicants (Volume 2A, Chapter 1)*).

For products authorised under the centralised procedure, the EC decision authorising a new therapeutic indication will record that it represents a significant clinical benefit in comparison with existing therapies following a scientific assessment by the EMA. For products authorised through other procedures, this is expected to be recorded in the public assessment report published after authorisation of a product (see section 6.2 of the *EC’s Notice to Applicants (Volume 2A, Chapter 1)*).

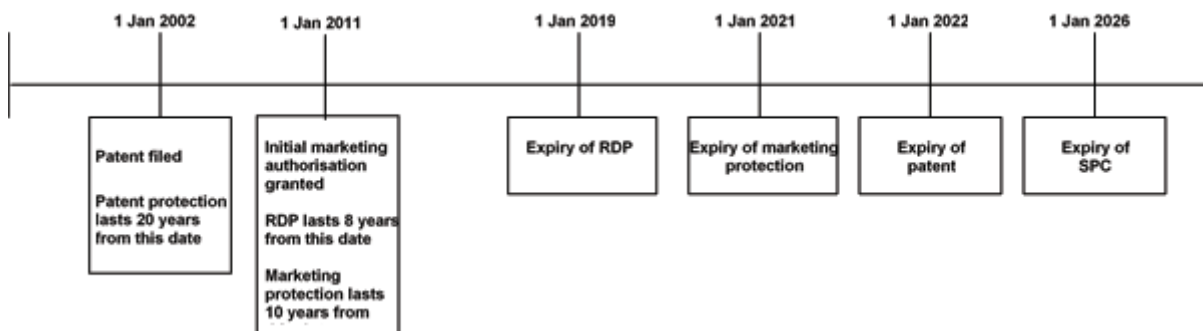
Medicinal products protected under previous rules

Medicinal products that were authorised as a result of EU centralised marketing authorisation applications submitted before 20 November 2005 and applications under the national, decentralised and mutual recognition procedures submitted before 30 October 2005 are protected by the rules that existed before the entry into force of the periods of protection provided for [Regulation \(EC\) 726/2004](#) and [Directive 2004/27/EC](#), which amends [Directive 2001/83/EC](#). Under the previous rules, a product benefited from either six or ten years of RDP depending on the territory in which it was authorised and there was no separate period of marketing protection. The RDP periods applicable to products for applications submitted are set out in section 6.1.3 of the [EC's Notice to Applicants \(Volume 2A, Chapter 1\)](#).

Interrelated periods: RDP and market protection versus patent and SPC protection

A simple example of the periods of protection that RDP, marketing protection, patents and SPCs can provide for pharmaceutical products are shown in the timeline below. For more information on SPCs, see [Practice note, Overview of Supplementary Protection Certificates](#).

Patents may be obtained at different stages of the R&D process and product lifecycle covering multiple aspects of a medicinal product such as the active substance itself, its first medical use, further medical uses, dosage regimes and pharmaceutical formulations. In respect of most innovative products, patents are typically filed earlier than when a marketing authorisation application is submitted and subsequently granted. In the example timeline below, the patent is granted on 1 January 2002, but the initial MA for the corresponding product is only granted nine years later, on 9 January 2011. This means that the marketing authorisation holder only has 11 years in which to benefit from its patent protection. RDP and marketing protection can therefore be of significant commercial value, in particular where they extend beyond the lifetime of the patent or SPC. Even in circumstances where they end before patent or SPC expiry, they can provide a stronger form of protection than the patent or SPC which may be more vulnerable to attack.



Furthermore, it is possible to obtain an extension of the period of marketing protection for:

- A new indication bringing significant clinical benefit (see [Significant clinical benefit](#)).
- Medicines that also have complied with an agreed paediatric investigation plan.
- Orphan medicinal products.

A paediatric extension to the term of SPC protection may also be available.

DEFINITION OF REFERENCE MEDICINAL PRODUCT?

The abridged routes provided in Articles 10(1), 10(2) and 10(3) of [Directive 2001/83/EC](#) are predicated on there being an appropriate “reference medicinal product” to which an abridged application can refer (see [Abridged applications](#)).

Article 10(2)(a) provides that a “reference medicinal product” is a “medicinal product authorised under Article 6, in accordance with the provisions of Article 8”. Article 10(1) of Directive 2001/83/EC also provides that a generic

product must be a generic of “a reference medicinal product which is or has been authorised under Article 6 ... in a Member State”.

The Court of Justice (ECJ) was asked to consider this definition in *Generics (UK) Ltd v Licensing Authority (Case C-527/07) EU:C:2009:379*. It ruled that for a product to function as a reference medicinal product it must have been authorised in accordance with EU law applicable at the time of the authorisation. This is on the basis that the abridged procedures cannot amount to a relaxation of safety and efficacy requirements by allowing a product to be authorised by reference to an earlier authorised product which did not meet the safety and efficacy requirements in force under EU law at the time of its authorisation. In order to ensure that these safety and efficacy requirements are satisfied, all the particulars and documents relating to a reference product and demonstrating its safety and efficacy should remain available to the competent authority.

Furthermore, it has been held as a general rule that the withdrawal of the marketing authorisation for a reference product for reasons other than those of public health does not prevent the future authorisation of a generic product and does not necessarily require an existing authorisation for a generic product to be withdrawn. However, if the withdrawal of the authorisation for the reference product is for public health reasons, the ECJ has said that a regulatory authority must be able to refuse to grant a generic marketing authorisation in such circumstances (*AstraZeneca A/S v Laegemiddelstyrelsen (Case C-223/01) EU:C:2003:546*). As part of the 2004 amendments to the EU pharmaceutical legislation, Article 10(1) of Directive 2001/83/EC was amended to codify the effect of the *AstraZeneca* decision as it now provides that a reference product can include one which “has been authorised”. However, the amendment goes further than the *AstraZeneca* decision as it removes the need for the reference medicinal product to be authorised at the time that the application for a generic marketing authorisation is lodged which the ECJ found was a requirement under *Directive 65/65/EEC* (the predecessor legislation to Directive 2001/83/EC).

The EC’s guidance is that any product which has been authorised in accordance with Articles 8(3) (full or full-mixed application), 10a (well-established use), 10b (fixed combinations) or 10c (informed consent) can act as a reference medicinal product (*section 5.3.1.1, EC’s Notice to Applicants (Volume 2A, Chapter 1)*).

Authorisations based on a full-mixed or well-established use application benefit from the 8+2(+1) approach, because the bibliographical references used to support such applications will typically be equally accessible to a third party applicant. However, a third party applicant may choose to conduct its own studies to supplement the bibliographic data in the case of a full-mixed application or rely on the references to published scientific literature to support its own well-established use application rather than waiting until expiry of the RDP period afforded to the earlier authorised product.

Generic and hybrid medicinal products

The EC’s guidance is that a product authorised in accordance with Articles 10(1) and 10(3) cannot act as a reference medicinal product (*section 5.3.1.1, EC’s Notice to Applicants (Volume 2A, Chapter 1)*). However, bridging data supporting a hybrid application approved under Article 10(3) for Product B (a modification of the reference medicinal product, Product A) does not benefit from RDP. Therefore, a subsequent third party’s Article 10(3) application for Product C (an equivalent modification of Product A) can use Product A as its reference medicinal product but also refer to the bridging data submitted in support of Product B. This is irrespective of whether the marketing authorisations for Products A and B are held by the same company and therefore belong to the same global marketing authorisation.

The EU courts have not ruled on any disputes where the marketing authorisation holders for Products A and B are not connected and therefore the products would not belong to the same global marketing authorisation under the current rules. However, the English High Court has adopted the same view as the EC, concluding that Sandoz was permitted to obtain a marketing authorisation for its transdermal buprenorphine patch, Reletrans (Product C), in an application under Article 10(3) in which the reference medicinal product was Temgesic, oral buprenorphine registered by Schering-Plough (Product A), and which also referred to bridging data submitted by Napp in support of its Article 10(3) application for its transdermal buprenorphine patch, BuTrans (Product B). In support of its application, the only new data supplied by Sandoz was data demonstrating that Reletrans was the bioequivalent

of BuTrans. Napp objected to Sandoz's reliance on the bridging data which it had submitted in its application for BuTrans which was data demonstrating the clinical effectiveness of BuTrans and its bioequivalence to Temgesic. Whipple J rejected Napp's argument that the bridging data it had submitted should be protected by RDP and refused to make a reference to the ECJ (*R (Napp Pharmaceuticals Ltd) v Secretary of State for Health acting as The Licensing Authority and another* [2016] EWHC 1982 (Admin)). Napp's application for permission to appeal was subsequently refused by the English Court of Appeal.

GLOBAL MARKETING AUTHORISATION

Before the amendments introduced by *Directive 2004/27/EC*, the ECJ had been asked to consider in several referrals made to it whether developments made to a product, for example, a new salt of the active or new formulation, should be entitled to a further period of RDP over and above that provided to the initial authorisation. Article 6(1) of *Directive 2001/83/EC* covers this issue expressly:

"When a medicinal product has been granted an initial marketing authorisation in accordance with the first sub-paragraph, 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)."

Therefore, the global marketing authorisation encompasses the original authorisation and later authorisations covering modifications of the type set out in Article 6(1). The RDP and marketing protection ends 8+2(+1) years from the date of the first authorisation of the global marketing authorisation and subsequent modifications of the type set out in Article 6 do not attract their own independent period of protection. As such the extent of the global marketing authorisation is crucial in determining the scope of any RDP from which a product may benefit.

In cases *Novartis Europharm v Commission (Case T-67/13) EU:T:2015:636* and *T-472/12 EU:T:2015:637*, the question that the General Court considered was whether Novartis' authorisation for Aclasta was to be considered to belong to the same global marketing authorisation as Zometa. Both products consisted of the same active substance (zoledronic acid) but were authorised in different therapeutic indications and strengths. Aclasta was not authorised as a variation to or extension of Zometa within the meaning of *Regulation (EC) 1085/2003* (but was granted a separate marketing authorisation pursuant to *Regulation (EEC) 2309/93* (the predecessor legislation to *Regulation (EC) 726/2004*)), had a different name than Zometa, and both medicinal products had separate entries in the Community Register of medicinal products. Despite this, the General Court held that Aclasta constituted an additional strength and a variation (consisting of new therapeutic indications) of Zometa, therefore falling within the scope of the global marketing authorisation concept in Article 6(1). On this basis, the General Court considered that Aclasta must belong to the same global marketing authorisation as Zometa and therefore was not entitled to an independent RDP period.

The ECJ dismissed Novartis' appeal of the decision of the General Court in joined cases *Novartis Europharm Ltd v European Commission (Cases C-629/15 P and C-630/15) EU:C:2016:1003*. In doing so, it ruled that the General Court was not wrong to refer to the previous case law of the ECJ (*Generics (UK) and others (Case C-368/96) EU:C:1998:583*, *Novartis Pharmaceuticals (Case C-106/01) EU:C:2004:245* and *Approved Prescription Services (Case C-36/03) EU:C:2004:781*) relating to the previous RDP regime before the 2004 amendments on the basis that there is continuity between the previous regime as it had been developed by the ECJ's case law and the current regime. Furthermore, the ECJ confirmed that it was irrelevant to the application of the global marketing authorisation concept whether later developments were authorised by: (i) separate marketing authorisations; or (ii) variations or extensions:

"It follows that that the concept of a 'global marketing authorisation', within the meaning of the second subparagraph of Article 6(1) of Directive 2001/83/EC, covers all subsequent developments of the original medicinal product, irrespective of their authorisation procedures, namely through the variation of the initial [marketing authorisation] for that medicinal product or through the grant of a separate [marketing authorisation]." (Paragraph 65.)

The EC's Notice to Applicants' states that for two marketing authorisations to fall within the same global marketing authorisation, they must satisfy two requirements (neither of which are expressly stated in Article 6(1)):

- The authorisations are held by the same marketing authorisation holder.
- The authorisations are for the same active substance.

The EU courts have not yet considered the EC's guidance in relation to the definition of same marketing authorisation holder and in relation to same active substance.

Same marketing authorisation holder

The EC's Notice to Applicants (section 2.8 of *EC's Notice to Applicants (Volume 2A, Chapter 1)*) provides the following guidance for determining whether two entities should be considered the "same marketing authorisation holder" for this purpose which extends beyond the marketing authorisation holders being the same legal person:

"An "applicant" and "marketing authorisation holder" can be a physical or legal entity. However, for the purposes of the application of the pharmaceuticals rules, having a distinct legal personality does not necessarily entail that each entity can be considered as a distinct applicant or marketing authorisation holder to the other one. In particular, it is noted:

- Applicants and marketing authorisation holders belonging to the same company group or that are controlled by the same physical or legal entity are to be considered as one entity.
- Applicants and marketing authorisation holders that do not belong to the same company group and are not controlled by the same physical or legal entity are to be considered as one applicant/marketing authorisation holder if they have concluded tacit or explicit agreements concerning the marketing of the same medicinal product for the purposes of the application of the pharmaceuticals rules regarding that medicinal product. This includes cases of joint marketing but also cases where one party licenses to the other party the right to market the same medicinal product in exchange for fees or other considerations."

New vs same active substance

The EC considers that two medicinal products must contain the same active substance for them to belong to the same global marketing authorisation. Therefore, if it can be considered that a product has a "new active substance", it does not belong to the same global marketing authorisation as that of a previously authorised medicinal product. There is no legislative definition of "new active substance" but the EC has provided a definition in Annex 1 to the *EC's Notice to Applicants (Volume 2A, Chapter 1)*:

"A new chemical, biological or radiopharmaceutical active substance includes:

- a chemical, biological or radiopharmaceutical substance not previously authorised in a medicinal product for human use in the European Union;
- an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised in a medicinal product for human use in the European Union but differing significantly in properties with regard to safety and/or efficacy from that chemical substance previously authorised;
- a biological substance previously authorised in a medicinal product for human use in the European Union, but differing significantly in properties with regard to safety and/or efficacy which is due to differences in one or a combination of the following: in molecular structure, nature of the source material or manufacturing process;
- a radiopharmaceutical substance which is a radionuclide, or a ligand not previously authorised in a medicinal product for human use in the European Union, or the coupling mechanism to link the molecule and the radionuclide has not been authorised previously in the European Union."

The definition in the second bullet point relating to modifications of chemical substances is the converse of the same active substance definition in Article 10(2)(b) in relation to generic medicinal products (see *Generic medicinal products*).

New active substance: combination products

Questions have arisen in practice when dealing with a medicinal product which contains:

- Active substances in a new fixed combination where those active substances were previously present in separate medicinal products or were previously present in combination with other active substances. For example:

- fixed combination consisting of active substances X+Y in Product 3 vs. active substance X in Product 1 and active substance Y in Product 2; or
 - fixed combination consisting of active substances X+Y in Product 2 vs. a fixed combination consisting of active substances X+Y+Z in Product 1.
- A single active substance which was previously only present within a fixed combination product. For example, active substance X in Product 2 vs. a fixed combination X+Y in Product 1.

In relation to new fixed combinations, the EC's guidance is that every new fixed combination of active substances is a new and unique medicinal product requiring a separate marketing authorisation, regardless of whether all the active substances contained therein were already authorised in a medicinal product or not. Each active substance within a fixed combination must have "documented therapeutic contribution within the combination" and therefore are considered different active substances when present in a particular fixed combination for the first time. On this basis, an authorisation for a new fixed combination does not belong to the global marketing authorisation of any of the previously authorised products containing the individual active substances. As such, a fixed combination product will benefit from RDP even if the marketing authorisation holder is also the holder of the marketing authorisation for the previously authorised products containing the individual active substances. The RDP for the fixed combination product will protect the data that is submitted in support of the safety and efficacy of the active substances when present as a fixed combination, that is, the results of new pre-clinical tests or new clinical trials relating to the fixed combination (see *Fixed Combination (Article 10b of Directive 2001/83/EC)*).

The view that a fixed combination is entitled to an independent period of RDP was challenged by Teva before the General Court (*Teva Pharma and Teva Pharmaceuticals Europe v EMA (Case T-547/12) EU:T:2014:1099*). However, Teva withdrew its challenge before there was a decision on the merits and so, at present, there has been no judicial decision on the issue.

Where a medicinal product consists of a single active substance which was present in a previously authorised fixed combination product, the EC's guidance is also that the medicinal product for the single active substance does not have the same active substance as contained in the previously authorised product and as such does not belong to the same global marketing authorisation as the previously authorised fixed combination product. The result of this is that the medicinal product for the single active substance benefits from an independent period of RDP on its authorisation even if the marketing authorisation holder is also the holder of the marketing authorisation for the previously authorised fixed combination product in which the active substance was present. In this situation, the RDP for the product containing the single active substance will protect the data that is submitted in support of the safety and efficacy of the active substance when present alone.

New active substance: biologics

As regards biologics, the EMA has not published any guidance on determining whether a biologic active substance that is a modification of a previously authorised substance is a new active substance. The EMA's guidance on biosimilars is that where an active substance has been intentionally changed to improve efficacy (commonly referred to as a "biobetter") it cannot be approved as a biosimilar. This suggests that such a substance is considered as a new active substance. For example, Teva's LONQUEX (lipegfilgrastim), a glycoPEGylated form of filgrastim whereby the PEG molecule was covalently attached to filgrastim via a carbohydrate linker, was considered to be a new active substance (and was authorised as a result of a full application) although a PEGylated form of filgrastim (NEULASTA (pegfilgrastim)) had previously been authorised which does not involve the use of a carbohydrate linker to attach the PEG molecule to filgrastim.

Assessment of new active substance status

In relation to modifications, the EC's guidance is that marketing authorisation applicants should make a request for a new active substance claim when filing their application and that an assessment of whether the "new active substance" definition is met should be carried out during the application procedure. The EMA has published two reflection papers on determining the new active substance status of chemical substances which provide guidance on, amongst other matters, the type of evidence that might be required to demonstrate the existence of a significant difference in safety or efficacy:

- *Reflection paper on the chemical structure and properties criteria to be considered for the evaluation of new active substance (NAS) status of chemical substances (17 December 2015).*
- *Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance (18 October 2012).*

The conclusion of whether a product contains a new active substance is recorded in the assessment report for a product and, in respect of centralised marketing authorisations, is also recorded in the EC decision granting the marketing authorisation.

The EC's guidance states that a "new active substance claim ... will not be considered retroactively" and that if an assessment report does not indicate that a product "contains a new active substance, it will be considered that the product at stake contains the same active substance and belongs to the global marketing authorisation of the already authorised medicinal product(s) as described in Article 6(1) of Directive 2001/83/EC."

However, given that the legislation does not require an applicant to make a new active substance claim, it is not clear what the legal effect of not making such a claim or of the regulatory authority's assessment of new active substance status (and the recordal of the EMA's assessment in that respect in an EC decision) is on entitlement to RDP. However, a practical effect might be that, unless a product is assessed as containing a new active substance, a regulatory authority will treat it as not benefiting from independent RDP and therefore will accept an abridged application referring to it provided that the RDP period that commenced on the initial authorisation belonging to the global marketing authorisation has elapsed. As such, the burden will be on the reference product marketing authorisation holder to challenge any decision granting such an abridged application on the basis of infringement of its RDP.

Examples of the scientific assessments that have been carried out in determining whether products contain a "new active substance" are Tecfidera, which contained an active substance that was present in a previously authorised product in combination with other substances, and *Aubagio*, which contained teriflunomide, a metabolite of a previously authorised active substance (leflunomide).

With respect to *Aubagio*, the EMA's Committee for Human Medicinal Products (CHMP) initially concluded that the evidence provided by the marketing authorisation applicant indicated that there were rather minor differences between teriflunomide and leflunomide with unknown or questionable clinical relevance. As such, the CHMP's initial conclusion was that the evidence did not justify concluding that teriflunomide qualifies as a new active substance. Following a request for re-examination of this conclusion, the CHMP maintained its conclusion that teriflunomide is a derivative of leflunomide but concluded by a majority opinion that there is a significant difference as regards safety between the two compounds based on the combination of biological plausibility and the non-clinical and clinical evidence available. Given this, the CHMP concluded that teriflunomide qualified as a new active substance ([EMA: European Public Assessment Report, Aubagio, International non-proprietary name: teriflunomide](#)).

In *Tecfidera*, the issue of whether Tecfidera contained a new active substance and/or belonged to the same global marketing authorisation as the previously authorised product, Fumaderm, raised novel issues for the CHMP and EC. Biogen sought a marketing authorisation for Tecfidera, which contained Dimethyl fumarate (DMF), the dimethyl ester of fumaric acid, for the treatment of multiple sclerosis. Biogen already held a marketing authorisation for Fumaderm which had been authorised in 1994 for the treatment of psoriasis and contained DMF plus calcium, magnesium and zinc salts of ethyl/ethyl hydrogen fumarate (MEF salts). Following a request for new active substance status, the CHMP carried out a review of the activity of the MEF salts and DMF. It found that: (i) the MEF salts and DMF are both pharmacologically active; (ii) the adverse events with DMF and Fumaderm are similar; and (iii) there were no head to head trials between DMF and Fumaderm because of the different indications. However, the CHMP concluded that DMF and the MEF salts are not the same active substance on the basis that they are both pharmacologically active agents which contain different therapeutic moieties. The EMA's European Public Assessment Report (EPAR) also stated that on this basis that DMF in Tecfidera is a new active substance.

Following discussion of the issue at the EU's Standing Committee on Medicinal Products, the EC granted a marketing authorisation for Tecfidera which recorded in a recital that Tecfidera and Fumaderm do not belong to the same global marketing authorisation. This was on the basis that because the MEF salts and DMF are not the same active substance (as opposed to DMF being considered a new active substance), Tecfidera which

only contains DMF is different from Fumaderm which contains both DMF and the MEF salts. As a result in the final EPAR, a footnote was added that in light of the discussion at the Standing Committee and the resulting EC decision, the conclusion that DMF in Tecfidera is a new active substance was obsolete.

On 13 February 2018, the UK High Court delivered a judgment rejecting a judicial review brought by Teva against the UK MHRA's decision to refuse to validate Teva's marketing authorisation application for a generic of Tecfidera on the basis that Tecfidera's RDP had not expired (*Teva BV, R (on the application of) v The Secretary of State for Health acting as the Licensing Authority and another* [2018] EWHC 228 (Admin)). In doing so, Mr Justice Jay held that the EC's assessment recorded in its marketing authorisation decision that Tecfidera does not belong to the same global marketing authorisation as Fumaderm was a binding decision that the MHRA had to follow in determining whether to accept Teva's marketing authorisation application. Although this conclusion was sufficient to dismiss Teva's challenge, the court also went on to consider Teva's case that the MHRA did not apply the relevant test for determining whether a substance is active, namely whether it exerts a clinically relevant effect in a particular product in the context of a particular indication and as such MEF salts should not be considered to be an active substance in Fumaderm. The effect of this would be that Tecfidera and Fumaderm contain the same active substance, DMF, and Tecfidera falls within the global marketing authorisation of Fumaderm. The judge also rejected this argument, finding that for a substance to be active it must be active in the medicinal product in question and it must be intended to bring or capable of bringing a pharmacological action which is in some way of benefit but it does not need to have a clinically relevant effect in the context of a particular indication. As such, the judge decided that the MHRA in fact applied the correct test in assessing whether the evidence provided by Teva showed that the MEF salts in Fumaderm were not active.

PARTICULARS TO ACCOMPANY AN APPLICATION FOR A MARKETING AUTHORISATION

EU pharmaceutical legislation provides for a number of different marketing authorisation application procedures and differing particulars that are required to be provided with these applications. The particulars that are required in full or full-mixed applications that are not required in abridged applications are the data that is protected by RDP and cannot be relied upon in an abridged application until the relevant RDP has expired.

Full or stand-alone applications

A full application for a marketing authorisation must be accompanied by the particulars set out in Article 8(3) of *Directive 2001/83/EC* in accordance with Annex 1 thereof, as amended. The scientific data required for a full application under Article 8(3) consists of:

- Pharmaceutical (physico-chemical, biological or microbiological) tests.
- Pre-clinical (toxicological and pharmacological) tests.
- Clinical trials.

“Full-mixed” applications

Rather than an applicant providing all of the required scientific data from their own pre-clinical tests or clinical trials, an application can consist of a combination of reports of limited non-clinical or clinical studies carried out by an applicant and of bibliographical references. Such applications, also referred to as “mixed” applications, should also be submitted under Article 8(3) of Directive 2001/83/EC. The requirements for such applications are provided in section 7 of Part II of Annex I to Directive 2001/83/EC.

Abridged applications

Applicants of following abridged procedures for obtaining a marketing authorisation are not required to submit all of the data set out in Article 8(3) and can instead rely on the data submitted in relation to a “reference medicinal product”:

- Generic applications (Article 10(1), Directive 2001/83/EC).
- Hybrid applications (Article 10(3), Directive 2001/83/EC).

- Biosimilar applications (Article 10(4), Directive 2001/83/EC).

Generic medicinal products

For a product to be authorised through the generic route, it must qualify as “a generic medicinal product” which is defined in Article 10(2)(b), Directive 2001/83/EC as:

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

The main criteria are therefore that a generic product must:

- Have the same qualitative and quantitative composition in active substances as the reference medicinal product (that is, the same active substances and same unit dose).
- Have the same pharmaceutical form as the reference medicinal product (Article 10(2)(b) specifically provides that the various immediate release oral dosage forms are considered the same pharmaceutical form for this purpose).
- Be bioequivalent with the reference medicinal product as demonstrated by appropriate bioavailability studies.

The definition of a “generic medicinal product” extends to products containing chemically modified forms of the active substance present in the reference product provided that there is no significant difference in safety and efficacy between the two forms. This can allow a generic manufacturer, for example, to obtain an authorisation for a generic product containing a chemically different form of the active substance to that present in the reference product where the particular form of the active substance present in the reference product is protected by a patent that is still in force following expiry of RDP.

Section 3 of Part II to Annex 1 of Directive 2001/83/EC describes such modifications of the active substance as being “the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative”. The issue of when two chemical substances are considered to be the “same active substance” is considered also in the context of the “global marketing authorisation” concept (see [Global marketing authorisation](#)).

“Hybrid” medicinal products

Hybrid applications made under Article 10(3) of Directive 2001/83/EC are termed as such because they rely in part on the data submitted for a reference medicinal product and in part on new data from appropriate pre-clinical tests and clinical trials. This new data is often referred to as “bridging data”.

Hybrid applications are required:

- Where the definition of “generic medicinal product” is not met.
- Where bioequivalence cannot be demonstrated through bioavailability studies.
- In cases of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration *vis-à-vis* the reference medicinal product.

Some guidance as to the types of studies that might need to be conducted to support a hybrid application is set out in Annex II to the [EC's Notice to Applicants \(Volume 2A, Chapter 1\)](#).

Biosimilars

Satisfying the definition of “generic medicinal product” (see [Generic medicinal products](#)) typically can only be met by medicinal products that contain chemical active substances. Biological medicinal products are significantly more complex molecules and it is not possible for a third party to reproduce identically the biologic active substance contained in a reference biologic medicinal product. Recognising that there will be differences between the version of the active substance in the reference product and the version of the same active substance in another product, Article

10(4) of Directive 2001/83/EC specifically provides a route for the authorisation of biological medicinal products that are “similar” to reference biological medicinal products, whereby such similarity is demonstrated by the applicant providing results from appropriate pre-clinical or clinical trials demonstrating such similarity.

Such similarity to the reference medicinal product needs to be demonstrated in relation to quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise. In practice, the level of data for a biosimilar application will be in between what is required for a generic application and a stand-alone application. Of critical importance in biosimilar applications are the scientific guidelines published by the EMA, in particular, the so-called overarching and product-specific guidelines.

Well-established use (Article 10a of Directive 2001/83/EC)

An application for a substance with a well-established medicinal use can be made according to Article 10a of Directive 2001/83/EC. Under this provision, the results of pre-clinical and clinical trials can be replaced entirely by detailed references to published scientific literature if it can be demonstrated that the active substance(s) of a medicinal product has been in well-established medicinal use in the claimed therapeutic indication within the EU for at least ten years, with recognised efficacy and an acceptable level of safety.

Fixed combination (Article 10b of Directive 2001/83/EC)

In an application for a fixed combination of active substances that have been used in previously authorised medicinal products but not previously in combination, only the results of new pre-clinical tests or new clinical trials relating to the fixed combination need to be provided. It is not necessary to provide scientific references relating to each individual active substance.

The EC’s guidance is that the individual active substances must have been authorised in accordance with EU law for the Article 10b route to be available (see section 5.5 of *EC’s Notice to Applicants (Volume 2A, Chapter 1)*).

Informed consent (Article 10c of Directive 2001/83/EC)

Under Article 10c, a marketing authorisation holder can consent to the use within the RDP period of its dossier for the purpose of an application for the authorisation of another medicinal product which has both:

- The same qualitative and quantitative composition in terms of active substances.
- The same pharmaceutical form as the already authorised product.

OTHER REGULATORY DATA PROTECTION PERIODS

Apart from RDP afforded to medicinal products authorised by a full marketing authorisation, RDP can also be granted to data from significant pre-clinical tests or clinical trials that have been submitted in support of either:

- A well-established substance being used for a new therapeutic indication.
- The change of classification of a medicinal product from prescription-only to over-the-counter.

New therapeutic indication for well-established substance

If an application is made for a new indication for a well-established substance, that is, a substance which can be shown to have a well-established medicinal use, where significant pre-clinical or clinical studies were carried out in relation to the new indication, a non-cumulative period of one year of RDP is granted (*Article 10(5), Directive 2001/83/EC*). According to the EC’s Notice to Applicants, because the RDP period is non-cumulative to other periods of protection, this RDP is separate to any other protection that the medicinal product may benefit from and only protects the data concerning the new indication (see section 6.3 of the *EC’s Notice to Applicants (Volume 2A, Chapter 1)*).

Guidance on what constitutes such significant pre-clinical or clinical studies has been published by the EC and is available on its website. The competent authority reviewing an application for a new indication for a well-established substance will determine if it is based on significant pre-clinical or clinical studies in accordance with this guidance.

An assessment that an application for a new indication is for a well-established substance and is based on significant pre-clinical or clinical studies will be recorded in the relevant EC decision granting the authorisation or national competent authority's public assessment report.

Change of classification (prescription-only medicine to OTC)

Data from significant pre-clinical tests or clinical trials, which have been submitted in support of a change of classification of a medicinal product from prescription-only to over-the-counter, are protected by one year of RDP such that this data cannot be referred to when examining an application by a third party for a change of classification of the same substance during that one-year period (*Article 74a, Directive 2001/83/EC*).

Guidance on what constitutes such significant pre-clinical or clinical studies has been published by the EC and is available on its website. The competent authority reviewing an application for a change of classification will determine if it is based on significant pre-clinical or clinical studies in accordance with this guidance.

An assessment that an application is based on significant pre-clinical tests or clinical studies will be recorded in the relevant EC or national decision authorising the change of classification.

ENFORCEMENT AND STANDING TO CHALLENGE GRANT OF GENERIC MARKETING AUTHORISATION

As regards centralised marketing authorisation procedures, a person may institute proceedings to annul an EC decision granting a marketing authorisation if it is of direct and individual concern to them under Article 263 of the *Treaty on the Functioning of the European Union*. This allows a marketing authorisation holder to bring an action for annulment in relation to the grant of a generic marketing authorisation which it contends infringes its RDP. Furthermore, where the EMA refuses to validate an application for a generic marketing authorisation on the basis that the application breaches a reference medicinal product's RDP, the generic applicant can bring an action for annulment of the refusal to validate because it constitutes a decision directly addressed to it.

On the other hand, an assessment by the EMA or letter from the EC before the adoption of a final decision on the grant of a marketing authorisation, for example, in relation to whether a product is regarded as containing a new active substance, is not considered to be an act intended to produce legal effects and therefore cannot be challenged before the EU courts (see, for example, *Sepracor v European Commission (Case C-477/11) EU:C:2012:292*).

As regards the right to challenge the grant of marketing authorisations before national courts, the ECJ held that Article 10 of *Directive 2001/83/EC* read in conjunction with Article 47 of the *Charter of Fundamental Rights of the EU* requires that the marketing authorisation holder for a reference product has the right to challenge the decision of a national competent authority to grant a generic marketing authorisation in order to seek judicial protection of the reference product's RDP or marketing protection (*Olainfarm AS (Case C-104/13) EU:C:2014:2316*). The relevant procedure for challenging such a decision is a matter of national law.

The ECJ has also issued a decision in the case of *Astellas Pharma (Case C-557/16) EU:C:2018:181*, that a competent authority of an EU member state, when adopting its decision to grant or refuse a generic marketing authorisation under the decentralised marketing authorisation procedure, cannot itself determine the point in time from which the data exclusivity period for the reference medicinal product starts to run. Once the competent authority of a member state has granted a generic marketing authorisation under the decentralised procedure, the court of that member state has jurisdiction to hear an action against the competent authority's decision to grant the generic marketing authorisation that is brought by the marketing authorisation holder of the relevant reference medicinal product. In addition, that court has jurisdiction to review the determination of the point in time from which the data exclusivity period for the reference medicinal product starts to run. By contrast, however, that court cannot review whether the initial marketing authorisation for the reference medicinal product granted in another member state was lawful (see *Legal update, National courts can review data exclusivity periods determined under the decentralised procedure (ECJ) (EU)*).