

Lunes de Patentes, Barcelona, 18 de setiembre de 2023

***IP Aspects of the
EU Pharma Law Reform***

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01

Aims and Proposals

EU Pharmaceutical Legislation Reform: Specific Objectives

- Make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines.
- Enhance security of supply and ensure medicines are always available to patients, regardless of where they live in the EU.
- Offer an attractive, innovation-and competitiveness friendly environment for research, development, and production of medicines in Europe.
- Make medicines more environmentally sustainable.

‘Innovation is not always focused on unmet medical needs, and there are market failures, especially in the development of priority antimicrobials that can help address antimicrobial resistance.’

Additional aims are ‘ensuring access to and continued supply of critical medicinal products during health crises’ or ‘facilitate early market entry of generic and biosimilar medicinal products, contributing to patient access and affordability’.



- Access
- Focus on unmet medical needs

Key IP related measures

- Introduction of variable incentives related to regulatory data protection and rewarding of innovation in areas of unmet medical needs.
- Introduction of incentive for repurposing off-patent, added value medicinal products.
- Increased competition from earlier market entry of generic and biosimilar medicinal products by:
 - ‘broadening’ the Bolar exemption
 - reduction of regulatory data and market protection periods and orphan market exclusivity



Key measures

- Introduction of variable incentives related to regulatory data protection and rewarding of innovation in areas of unmet medical needs.
- Introduction of incentive for repurposing off-patent, added value medicinal products.
- Increased competition from earlier market entry of generic and biosimilar medicinal products by:
 - 'broadening' the Bolar exemption
 - reduction of regulatory data and market protection periods and orphan market exclusivity
 - simplifying the procedures for the authorisation of generics and biosimilars
 - better recognizing interchangeability of biosimilars with their reference medicinal products
- Simplify the authorization system: reduce time of evaluation, avoid renewal of authorizations every 5 years or sunset clause, reduce the number of committees at the EMA, envisaged use of the electronic product information (as opposed to paper leaflets), etc.
- Strengthen control and implement mechanisms to reduce shortage of medicinal products
- Increase the requirements to reduce the environmental risk associated with medicines...

IP related

Not IP related

Changes

General
pharma
legislation

Specific
pharma
legislation

Current Pharma Legislation

Directive 2001/83/EC
(med. products for human use)

Regulation (EC) No 726/2004
(Community procedures and EMA)

Regulation (EC) No 1901/2006
(the 'Paediatric Regulation')

Regulation (EC) No 141/2000
(the 'Orphan Regulation')

Regulation (EC) No 1394/2007
Advanced Therapy Medicinal
Products (ATMP) Regulation

Proposed Pharma Legislation

'New Directive' - COM(2023) 192 final

'New Regulation' - COM(2023) 193 final

Both proposals published on 26 April 2023

general framework for the authorisation
and SPC extension rewarding

procedural requirements
and PUMA rewarding



Broadening of the scope of the centralised procedure

Recital (10) of New Reg

(10) With a view to maintain a high-level of scientific evaluation for new medicinal products and medicinal products that will serve the entire Union population, the centralised procedure should be mandatory for high-technological medicinal products, particularly those resulting from biotechnological processes, priority antimicrobials, orphan medicinal products, paediatric use medicinal products [PUMAs] and any medicinal product that includes an active substances not authorised before the last important change to the scope of the centralised procedure in 2004.

Broadening of the scope of the centralised procedure

Annex I: MEDICINAL PRODUCTS TO BE AUTHORISED BY THE UNION of New Reg

ANNEX I: MEDICINAL PRODUCTS TO BE AUTHORISED BY THE UNION

1. Medicinal products developed by means of one of the following biotechnological processes:
 - recombinant nucleic acid technology;
 - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells.
2. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007.
3. **Medicinal products for human use containing an active substance which on 20 May 2004 was not authorised in the Union, excluding allergen products or herbal medicinal products, which shall in any case not be authorised by the Union.**
4. Medicinal products that are designated as orphan medicinal products pursuant to this Regulation.
5. Medicinal products authorised in accordance with a paediatric use marketing authorisation. [PUMA]
6. Priority antimicrobials as referred to in Article 40.

Agenda

- The new Bolar exemption
- Changes in the regulatory data protection and market protection periods
- Amended incentives for orphan medicines
- Incentives for paediatric medicines
- New vouchers for priority antimicrobials addressing antimicrobial resistance.



02

The new Bolar exemption

Bolar exemption in the current directive

Article 10 (6)

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

paragraphs 1 and 2: generic medicinal products

paragraph 3: hybrids

paragraph 4: biosimilars or bio-hybrids ('similar biologic product')

Legal basis: Art 10(6) Current Dir

Proposed Bolar exemption

Article 85: Exemption to the protection of intellectual property rights

Patent rights, or supplementary protection certificates under the [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted] shall not be regarded as infringed when a reference medicinal product is used for the purposes of:

- (a) studies, trials and other activities conducted to generate data for an application, for:
 - (i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;
 - (ii) health technology assessment as defined in Regulation (EU) 2021/2282;
 - (iii) pricing and reimbursement.
- (b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

[Legal basis: Art 85 New Dir](#)

Proposed Bolar exemption

Recitals 63 and 64 New Dir

- (63) It is currently possible for applicants for marketing authorisation of generic, biosimilar, hybrid and bio-hybrid medicinal products to conduct studies, trials and the subsequent practical requirements necessary to obtain regulatory approvals for those medicinal products during the term of protection of the patent or Supplementary Protection Certificate (SPC) of the reference medicinal product, without this being considered patent or SPC infringement. The application of this limited exemption is however fragmented across the Union and it is considered necessary, in order to facilitate the market entry of generic, biosimilar, hybrid and bio-hybrid medicinal products that rely on a reference medicinal product, to clarify its scope in order to ensure a harmonised application in all Member States, both in terms of beneficiaries and in terms of activities covered. The exemption must be confined to conduct studies and trials and other activities needed for the regulatory approval process, health technology assessment and pricing reimbursement request, even though this may require substantial amounts of test production to demonstrate reliable manufacturing. During the term of protection of the patent or SPC of the reference medicinal product, there can be no commercial use of the resulting final medicinal products obtained for the purposes of the regulatory approval process.
- (64) It will allow, inter alia, to conduct studies to support pricing and reimbursement as well as the manufacture or purchase of patent protected active substances for the purpose of seeking marketing authorisations during that period, contributing to the market entry of generics and biosimilars on day one of loss of the patent or SPC protection.

Proposed Bolar exemption

Explanatory Memorandum, page 17

The 'Bolar exemption' (under which studies can be carried out for subsequent regulatory approval of generics and biosimilars during the patent or supplementary protection certificate protection of the reference medicinal product), will be broadened in scope and its harmonised application in all Member States ensured.

Current Bolar exemption

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

Proposal

Patent rights, or supplementary protection certificates [...] shall not be regarded as infringed when a reference medicinal product is used for the purposes of:

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Patented active substance

Proposal

Patent rights, or supplementary protection certificates [...] shall not be regarded as infringed when a reference medicinal product is used for the purposes of:

- (a) studies, trials and other activities conducted to generate data for an application, for:
 - (i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;
 - (ii) health technology assessment as defined in Regulation (EU) 2021/2282;
 - (iii) pricing and reimbursement.
- (b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

Current Bolar exemption

6. Conducting the necessary studies and trials with a view to the application of paragraphs 1, 2, 3 and 4 and the consequential practical requirements shall not be regarded as contrary to patent rights or to supplementary protection certificates for medicinal products.

Active Pharmaceutical Ingredients = 'active substances' are not mentioned and have a different definition to 'medicinal products'.

Proposal

Patent rights, or supplementary protection certificates [...] shall not be regarded as infringed when a reference medicinal product is used for the purposes of: ~?

(a) studies, trials and other activities conducted to generate data for an application, for:

(i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;

(ii) health technology assessment as defined in Regulation (EU) 2021/2282;

(iii) pricing and reimbursement.

(b) the activities conducted exclusively for the purposes set out in point (a). may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

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 - (iii) pricing and reimbursement.
- (b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

Definitions of medicinal products and active substances

- (1) 'medicinal product' means any substance or combination of substances that fulfils at least one of the following conditions:
- (a) any substance or combination of substances that is presented as having properties for treating or preventing disease in human beings; or
 - (b) any substance or combination of substances that may be used in or administered to human beings with a view to either restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis;
- ...
- (3) 'active substance' means any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis;

Legal basis: Art 4 New Dir

Bolar Exemption in the Spanish Patent Law

Current Bolar exemption

Artículo 61. Límites generales y agotamiento del derecho de patente.

1. Los derechos conferidos por la patente no se extienden:

...

c) A la realización de los estudios y ensayos necesarios para obtener la autorización de comercialización de medicamentos en España o fuera de España y los consiguientes requisitos prácticos, incluida la preparación, obtención y utilización del principio activo para estos fines.

Proposal

(i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations

Bolar Exemption in the UPCA

Current Bolar exemption at the UPCA

ARTICLE 27: Limitations of the effects of a patent

The rights conferred by a patent shall not extend to any of the following:

...

(d) the acts allowed pursuant to Article 13(6) of Directive 2001/82/EC or Article 10(6) of Directive 2001/83/EC in respect of any patent covering the product within the meaning of either of those Directives;

...

Proposal

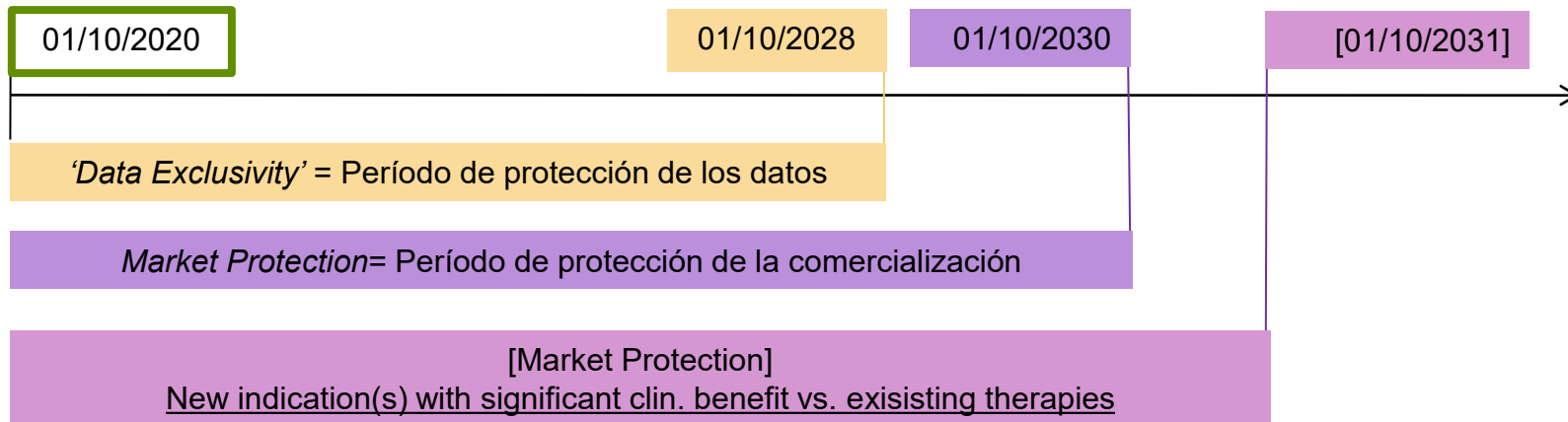
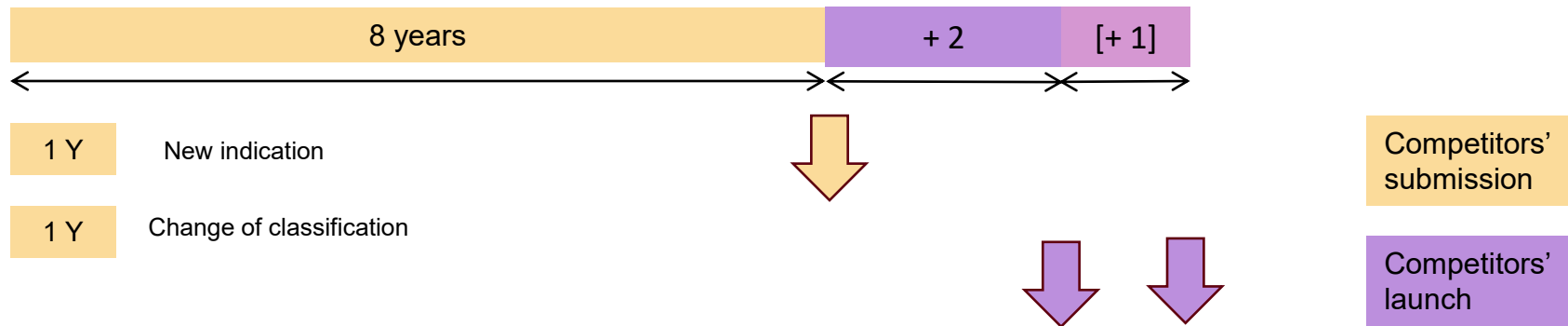
At the application date of the New Directive the text of the proposal will automatically replace the existing Bolar clause at the UPCA by the fact that the old directive will be repealed.

03

Changes in the
regulatory data protection and
market protection periods

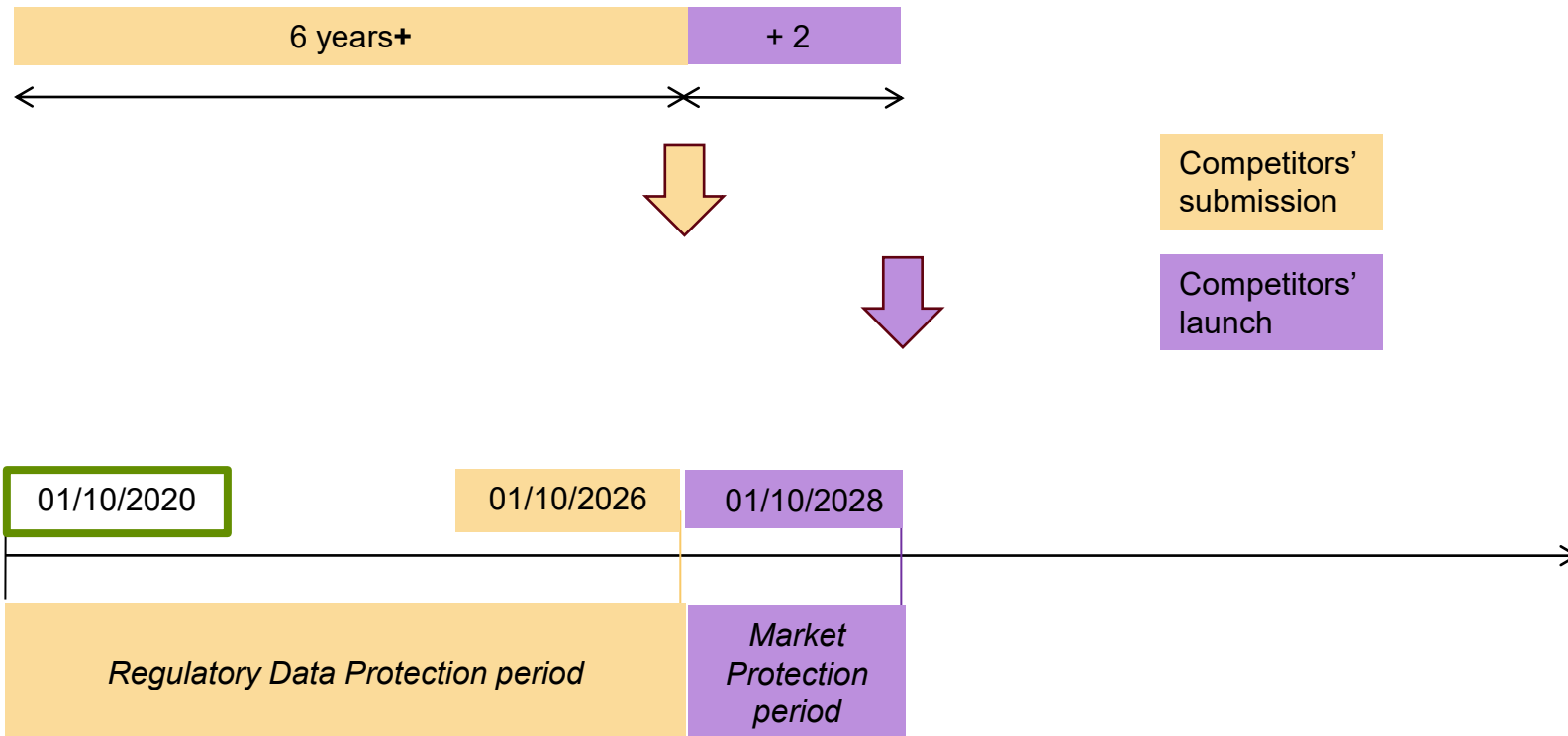
Current regulatory data and market protection: 8+2[+1]

Example: reference product (originator) aproved on 1 October 2020

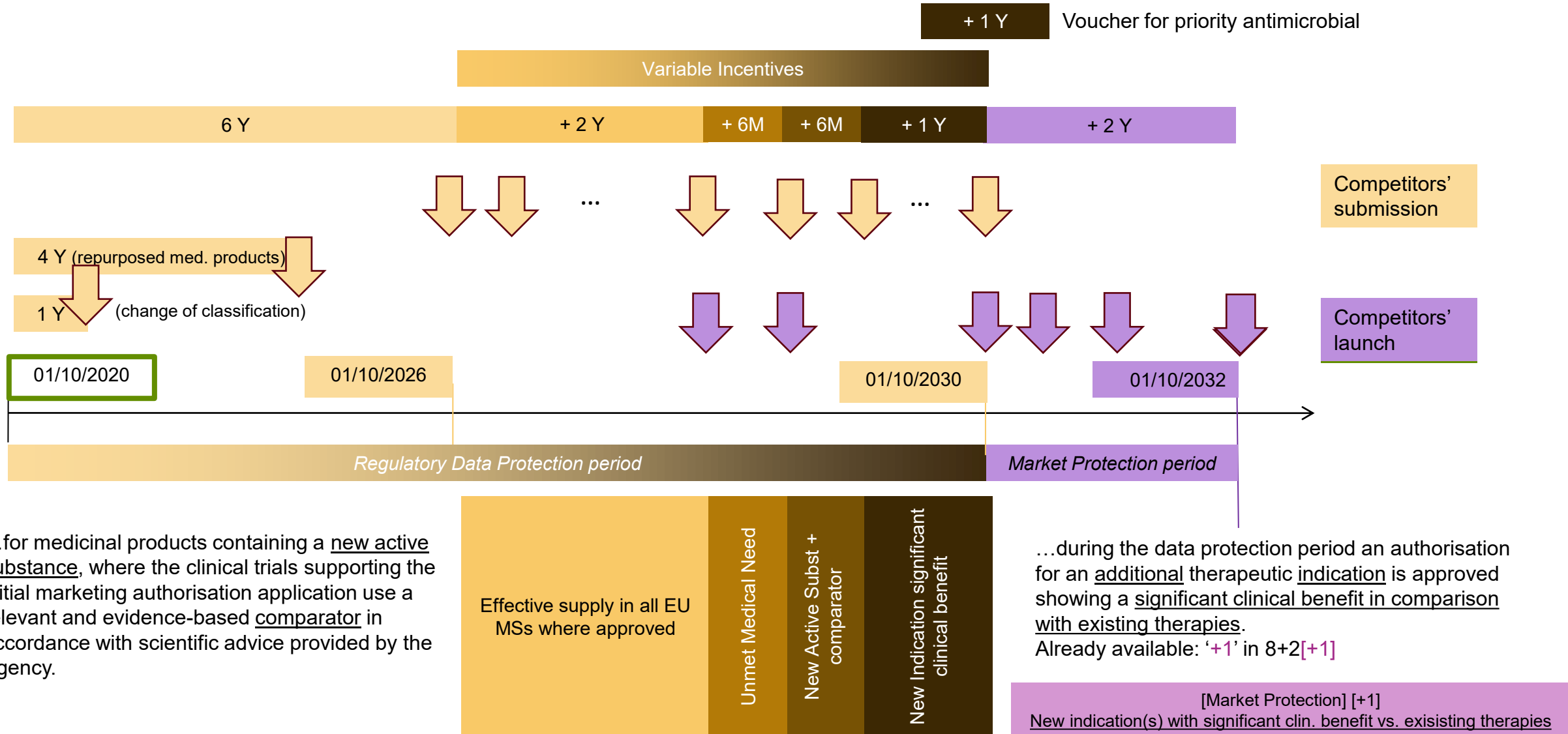


Proposed regulatory data and market protection

Example: reference product (originator) approved on 1 October 2020. Without variable incentives.



Proposed regulatory data and market protection



...for medicinal products containing a new active substance, where the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency.

Effective supply in all EU MSs where approved	Unmet Medical Need	New Active Subst + comparator	New Indication significant clinical benefit
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...during the data protection period an authorisation for an additional therapeutic indication is approved showing a significant clinical benefit in comparison with existing therapies.
 Already available: '+1' in 8+2[+1]

[Market Protection] [+1]
 New indication(s) with significant clin. benefit vs. existing therapies

Effective supply in all EU MSs where approved

2 additional years of regulatory data protection period.

The holder must demonstrate that:

'medicinal products are released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid'

This must be fulfilled within two years, from the date when the marketing authorisation was granted or, within three years from that date for:

- (i) SMEs;
- (ii) not-for-profit entities; and
- (iii) companies that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations (if they belong to a group of companies, this applies to the group).



Effective supply in all EU MSs where approved

- Only available for products that have been granted:
 - a centralised marketing authorisation, or that have been granted
 - a national marketing authorisation through the decentralised procedure (not for mutual recognition or purely national procedures).
- Under the decentralised procedure states not designated by the holder can request to enter the procedure!
- A variation must be submitted to show that conditions are met.
- Waivers for some states are possible by issuing a statement of non-objection to prolong the period of regulatory data protection.

Legal bases: Art 81(2)(a) and Art 82 of New Directive

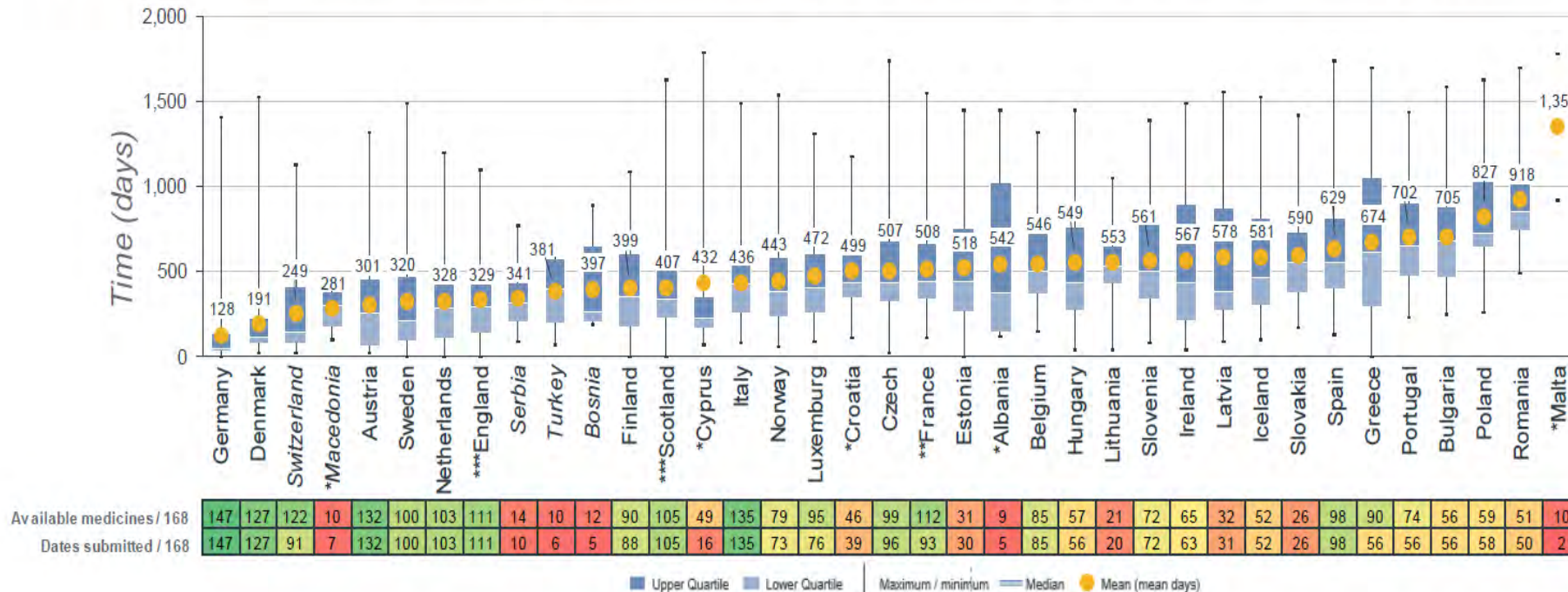


Effective supply in all EU MSs achievable?

Effective supply in all EU MSs where approved

Time to availability (2018-2021)

The **time to availability** is the days between marketing authorisation and the date of availability to patients in European countries (for most this is the point at which products gain access to the reimbursement list[†]). The marketing authorisation date is the date of central EU authorisation in most countries, except for countries shown in italics where local authorisation dates have been used. Data is correct to 5th January 2023.



Source: EFPIA Patients W.A.I.T. Indicator 2022 Survey, April 2023, page 14

Effective supply in all EU MSs achievable?

...[S]everal EU Member States cannot complete a pricing discussion before a developer has completed P&R processes in a number of other countries (the so-called “external reference pricing” system).

Examples of this practice include Bulgaria, which requires five (5) markets to be funding a therapy before they will engage in P&R discussions, as well as Romania which requires twelve (12) markets to have reached a pricing agreement with public prices before P&R negotiation begins.

A consequence of this policy is that it can lead to delays or longer timelines for therapies to be launched in specific Member States.

...

Small or non-existent patient populations in the case of rare diseases ...mean launching in all Member States would not be technically feasible.

Source:

Feedback from: European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

[Feedback from: European Confederation of Pharmaceutical Entrepreneurs \(EUCOPE\)](#)

europa.eu

Effective supply in all
EU MSs where approved

Effective marketing in all EU MSs where approved

Effective supply in
all EU MSs where
approved

2 additional years of regulatory data protection period.

Art 81(2) New Dir: Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:

- (a) **24 months**, where the marketing authorisation holder demonstrates that the conditions referred to in Article 82(1) are fulfilled within two years, from the date when the marketing authorisation was granted or, within three years from that date for any of the following entities:
- (i) SMEs within the meaning of Commission Recommendation 2003/361/EC;
 - (ii) entities not engaged in an economic activity ('not-for-profit entity'); and
 - (iii) undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part, since the establishment of the undertaking or the group, whichever is earliest.

Art 82(1) The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.

The prolongation referred to in the first subparagraph shall apply to medicinal products that have been granted a centralised marketing authorisation, as referred to in Article 5 or that have been granted a national marketing authorisation through the decentralised procedure, as referred to in Chapter III, Section 3.

[Legal bases: Art 81\(2\)\(a\) and Art 82 of New Directive](#)

Unmet Medical Need

6 additional months of regulatory data protection period if at the time of the initial marketing authorisation application the medicinal product addresses an unmet medical need:

- A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:
 - (a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;
 - (b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

- Designated orphan medicinal products shall be considered as addressing an unmet medical need.

The Agency will adopt scientific guidelines for the application of this Article.



Unmet Medical Need

Art 81(2) New Dir

(b) six months, where the marketing authorisation applicant demonstrates at the time of the initial marketing authorisation application that the medicinal product addresses an unmet medical need as referred to in Article 83

Article 83 New Dir: Medicinal products addressing an unmet medical need

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

- (a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;
- (b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. Designated orphan medicinal products referred to in Article 67 of [revised Regulation (EC) No 726/2004] shall be considered as addressing an unmet medical need.

3. Where the Agency adopts scientific guidelines for the application of this Article it shall consult the Commission and the authorities or bodies referred to in Article 162 of [revised Regulation (EC) No 726/2004].

New Active Substance + clinical trials with relevant comparator

Art 81 New Dir

2. ...

(c) six months, for medicinal products containing a new active substance, where the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency;

3. The Agency shall set the scientific guidelines referred to in paragraph 2, point (c), on criteria for proposing a comparator for a clinical trial, taking into account the results of the consultation of the Commission and the authorities or bodies involved in the mechanism of consultation referred to in Article 162 of [revised Regulation (EC) No 726/2004].

Additional indication showing significant clinical benefit

Art 81(2) New Dir

(d) 12 months, where the marketing authorisation holder obtains, during the data protection period, an authorisation for an additional therapeutic indication for which the marketing authorisation holder has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies.

Existing incentive: In the current legislations it extends the market exclusivity, 8+2[+1]. In the proposal, it extends the regulatory data protection period.

[Market Protection] [+1]

New indication(s) with significant clin. benefit vs. existing therapies

Data protection for repurposed medicinal products

4 Y (repurposed med. products)

A regulatory data protection period of **four years** shall be granted for a medicinal product with respect to a new therapeutic indication if:

- (a) adequate non-clinical or clinical studies demonstrate significant clinical benefit, and
- (b) the medicinal product is authorised as generic, hybrid, biosimilar or bio-hybrid [Note: not a variation of an innovative product] and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation.

The data protection period may only be granted once for any given medicinal product.

Legal bases: Article 84 (New Dir)

Data protection for repurposed medicinal products

Current data exclusivity for 'well-established substances'

1 Y

Art 10(5) of Directive 2001/83/EC

In addition to the provisions laid down in paragraph 1, where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity will be granted,

provided that significant pre-clinical or clinical studies were carried out in relation to the new indication."

The data exclusivity period is non-cumulative to other periods of protection: it refers exclusively to the data concerning the new indications.

Comments:

The first paragraph of Art 10 establishes 8+2+1 (data/market exclusivity). 'Well-established substance' is defined in Annex I, Part II.1.a. of Directive 2001/83/EC

Proposed extended exclusivity

4 Y (repurposed med. products)

A regulatory data protection period of **four years** shall be granted for a medicinal product with respect to a new therapeutic indication if:

- (a) **adequate non-clinical or clinical studies demonstrate significant clinical benefit, and**
- (b) the medicinal product is authorised as generic, hybrid, biosimilar or bio-hybrid [Note: not a variation of an innovative product] and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation.

The data protection period **may only be granted once** for any given medicinal product.

Based on Article 84 (New Dir)

Data protection for repurposed medicinal products

Article 84 (New Dir): Data protection for repurposed medicinal products

1. A regulatory data protection period of **four years** shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that:
 - (a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and
 - (b) the medicinal product is authorised in accordance with Articles 9 to 12 [generic, hybrid, biosimilar or bio-hybrid] and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.
2. The data protection period referred to in paragraph 1 **may only be granted once** for any given medicinal product.
3. During the data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorised with an additional therapeutic indication.

Data protection of evidence for the change of prescription status: 1 year (no change)

Article 55: Data protection of evidence for the change of prescription status (New Dir)

Where a change of prescription status of a medicinal product has been authorised on the basis of significant non-clinical tests or clinical studies, the competent authority shall not refer to the results of those tests or studies when examining an application by another applicant for or marketing authorisation holder for a change of prescription status of the same substance for one year after the initial change was authorised.

No change with regards to Article 74a of Directive 2001/83/EC

Transitional provisions for 'regulatory data protection periods' in the New Regulation

Article 181: Entry into force (New Reg)

This Regulation shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

It shall apply from [Note to the OP: Please insert the date of 18 months after its entry into force. The date should be identical to the date for the application of the Directive].

Article 180: Transitional provisions (New Reg)

4. By way of derogation, the periods of regulatory protection referred to in Article 29 shall not apply to reference medicinal products for which an application for marketing authorisation has been submitted before [Note to the OP: Please insert the **date of application** of this Regulation]. Article 14(11) of Regulation (EC) No 726/2004 shall continue to apply to them.

[Products submitted before the date of application remain on the old data exclusivity provisions (8+2+[+1]).]

Transitional provisions for 'regulatory data protection periods' in the New Directive

Article 218: Transitional provisions (New Dir)

5. By way of derogation from Article 81, reference medicinal products for which the application for marketing authorisation has been submitted before [OP please insert the date = 18 months after the date of entering into force of this Directive] shall be subject to the provisions on data protection periods set out in Article 10 of Directive 2001/83/EC as applicable on [OP please insert the date = 18 months after the date of entering into force of this Directive] until [OP please insert the date = 18 months after the date of entering into force of this Directive].

[I do not understand this wording, it seems confusing and wrong. The idea must be that that products submitted before date of application remain on the old data exclusivity provisions (8+2+[+1]) as under the New Reg]

Transitional provisions for 'regulatory data protection periods' in the New Directive

Article 218: Transitional provisions (New Dir)

5. By way of derogation from Article 81, reference medicinal products for which the application for marketing authorisation has been submitted before 30/07/2027 shall be subject to the provisions on data protection periods set out in Article 10 of Directive 2001/83/EC as applicable on 30/07/2027 until 30/07/2027.

[To simplify the wording I have set that the application date would be 30/07/2027.

I do not understand this wording, it seems confusing and wrong. The idea must be that that products submitted before date of application remain on the old data exclusivity provisions (8+2+[+1]) as under the New Reg]

Transitional provisions for [orphan] market exclusivity

None found?!

Was the intention of the drafters to apply the new provisions to all products from the date of application?

Thank for your attention

Thanks to Ferrer's Patent Team for comments and ideas.
Opinions expressed are those of the author only and may not represent the stance of Ferrer.

04

Amended incentives for
orphan medicines

Reasons for limitations of incentives of [orphan] market exclusivity

As regards the Regulation's design, market exclusivity is the main incentive it provides. While the evaluation provides no evidence that might cast doubt on the market exclusivity concept as such, it exemplifies the weaknesses of a one-size-fits-all incentive. The findings of the evaluation suggest that for the 73% of orphan medicines the market exclusivity reward has helped to increase profitability for these products, without overcompensating the sponsor. However, for the 14% of orphan medicines, the 10-year market exclusivity may have led to overcompensation. Hence the 10-year exclusivity is thus not fully justified for certain orphan medicines. These are often well-established use products, or medicines authorised for multiple orphan conditions.

Under 'Conclusions', on page 102; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION;

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Reasons for the market exclusivity change from ‘prevent filing’ to preventing approval

Generic competition, according to the evaluation study, has only been observed for very few products to date. As market protection incentives will only expire in the coming years for several authorised orphan medicines, it seems likely that there will be increased generic entry from that moment. For orphan medicines, however, the literature suggests a slower price fall upon generic entry in comparison to other medicines. Among other factors, this may be because **an application for a generic of an [orphan medicine] can be submitted i.e. only on the day the exclusivity period of the orphan medicine expires.**

Under ‘Conclusions’, on page 103; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION;

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Reasons for the changes in the criteria of orphan medicines

While the Regulation includes a mechanism to reduce the exclusivity period if a product is deemed to be profitable, the conditions under which the market exclusivity can be reduced to six years ex post are difficult to apply and rarely used. This finding goes hand-in-hand with the fact that only one application has been received under the 'insufficient return on investment' criterion, and that was subsequently withdrawn. This has shown that it is hard to estimate future investments and the returns on them in advance, before the therapeutic indications for which the product may be used have been established, and before the price at which it is to be sold is clear.

In recent years, it has been suggested that the 'insufficient return on investment criterion' could be used by developers in the field of novel antimicrobials. However, so far it has failed to attract companies, despite the unmet need and the clear market failure in this area.

Under 'Conclusions', on page 103; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION;

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Reasons for the changes in the criteria of orphan medicines

(90) Objective criteria for the orphan designation based on the prevalence of the life-threatening or chronically debilitating condition for which diagnosis, prevention or treatment is sought and the existence of no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union should be maintained; a prevalence of not more than five affected persons per 10 000 is generally regarded as the appropriate threshold. **The orphan designation criterion on the basis of return on investment has been abolished, since it has never been used.**

Recital 90 of New Reg

Reasons for the limitation of rewards for several orphan indications for the same active substance

The Regulation's potential inefficiencies and undesirable consequences were identified in certain cases. There are 22 orphan products authorised for two or more orphan indications, each referring to distinct orphan conditions, which are entitled to multiple periods of market exclusivity ('**indication stacking**'). Although it is desirable to broaden the therapeutic areas for which an orphan medicine can be used and this should be encouraged to serve patients in need. However, it is often **unclear whether the additional market exclusivity period was needed to recover the additional costs of R&D**. Additional orphan indications have been also identified as a barrier to developing generic orphan medicines. However, the overall 'inefficiency' is limited as the number of products authorised for multiple orphan indications in the EU is relatively small, and in most cases there is a very big overlap in the periods of market exclusivity for each indication. Finally, indication stacking should be seen in the light of advances in personalised medicine.

Under 'Conclusions', on page 103; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION;

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Reasons for the reduced market exclusivity for well-established products

Medicines that were in well-established use as a magistral or officinal formula before their authorisation as orphan medicines, or which are repurposed established medicines, account for 19% of orphan medicines in the EU. This is a lower figure than in the US. However, recent cases in which producers substantially increased the price of a newly-authorized orphan medicine that was already available to patients as a magistral or officinal formula, at a much lower price, have raised questions about this authorisation route. These price increases seem to bear no relation to actual R&D costs. Although price setting lies beyond the remit of the orphan Regulation, additional market exclusivity seems to be the main factor influencing monopolistic price setting in these cases. Consideration should therefore be given to the possibility of the Regulation's providing differentiated incentives, depending on the type of application for marketing authorisation or the level of investment in R&D.

Under 'Conclusions', on pages 103-104; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION; Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

Impact of orphan changes

The total balance of yearly costs and benefit calculated per interested stakeholder group for this preferred option compared to the baseline are: EUR 662 million cost savings for public payers from accelerated generic entry and a EUR 88 million profit gain for the generic industry. The public will benefit from additional 1 or 2 HUMN medicinal products and overall broader and faster access for patients. **Originators will see an estimated EUR 640 million gross profit loss from earlier generic entry**, but savings are expected for companies through the cross-cutting measures in the general pharmaceutical legislation that would allow for better coordination, simplification and accelerated regulatory processes.

Pages 12-13 of Explanatory Memorandum of New Reg, under 3. RESULTS OF EX-POST EVALUATIONS, STAKEHOLDER CONSULTATIONS AND IMPACT ASSESSMENTS; / Impact assessments / Orphan and paediatric legislation

Orphan reassessment at 6 years: abolished

(102) ...In order to ensure increased predictability for developers, the possibility to review the eligibility criteria for market exclusivity after six years after the marketing authorisation has been abolished.

Recital 102 New Reg

Criteria for orphan designation

Current law

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:
 - (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and
 - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

Legal basis: Art 3 Current Orphan Reg

Proposal

Article 63: Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:
 - (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted;
 - (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.
2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

Legal basis: Art 63 New Reg

Criteria for orphan designation

Current law

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:
 - (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and
 - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

Legal basis: Art 3 Current Orphan Reg

Proposal

Article 63: Criteria for orphan designation

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Legal basis: Art 63 New Reg

Criteria for orphan designation

Current law

Article 3

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 - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

Legal basis: Art 3 Current Orphan Reg

Proposal

Article 63: Criteria for orphan designation

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Legal basis: Art 63 New Reg

Criteria for orphan designation

Current law

Article 3

Criteria for designation

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 - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

Prevalence
criterion

Proposal

Article 63: Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:
 - (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted; there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.
2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

Legal basis: Art 3 Current Orphan Reg

Legal basis: Art 63 New Reg

Criteria for orphan designation

Current law

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:
 - (a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment; and
 - (b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition

insufficient
return on
investment
criterion

Legal basis: Art 3 Current Orphan Reg

Proposal

Article 63: Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:
 - (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted;
 - (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.
2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

Designation criteria

Legal basis: Art 63 New Reg

Criteria for orphan designation

Article 63: Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:
 - (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted;
 - (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.
2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.
3. The Commission shall adopt the necessary provisions for implementing this Article by means of implementing acts in accordance with the procedure laid down in Article 173(2) in order to further specify the requirements referred to in paragraph 1.

Criteria for orphan designation: significant benefit

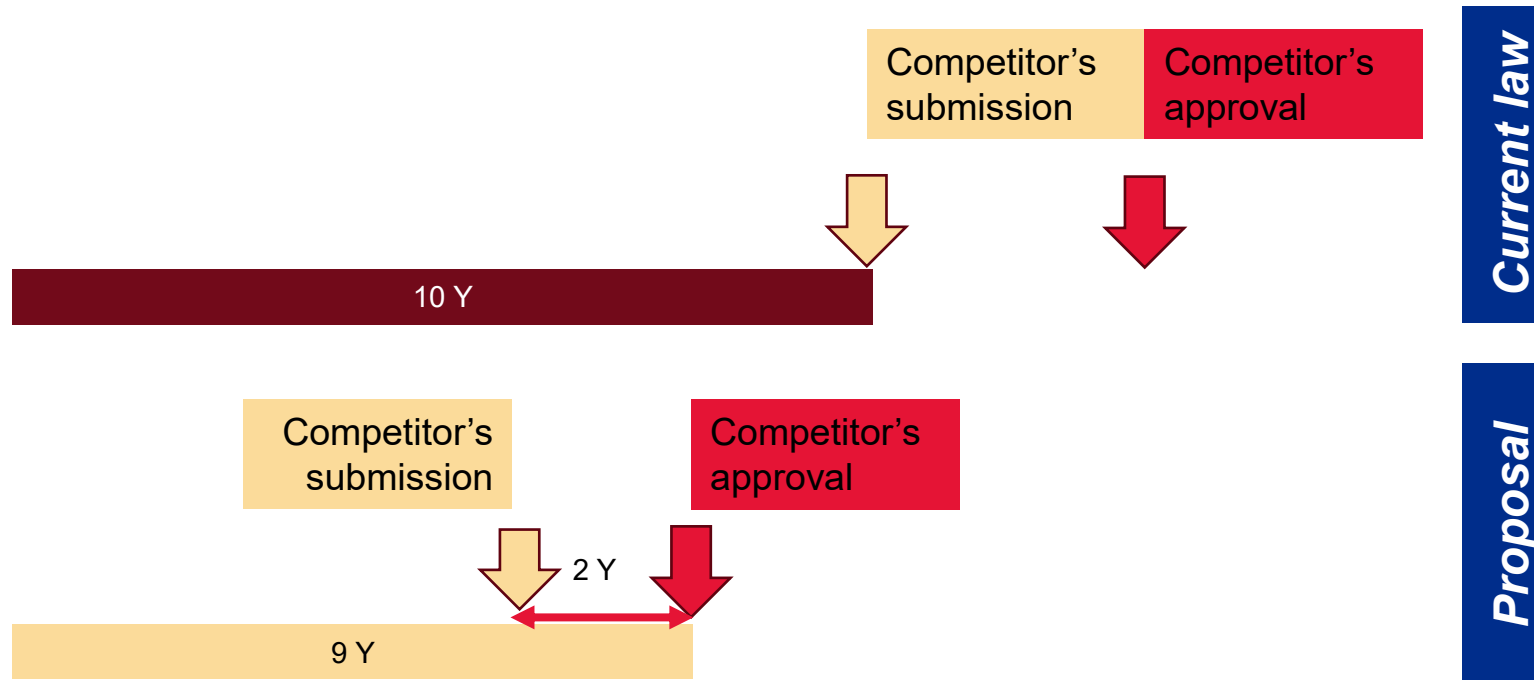
Article 63: Criteria for orphan designation

...where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.

Article 2 (7) 'significant benefit' means a clinically relevant advantage or a major contribution to patient care of an orphan medicinal product if such an advantage or contribution benefits a substantial part of the target population;

Legal basis: Art 63 New Reg, Art 2(7) Definitions

Market exclusivity effective length reduction



Effective protection will be significantly reduced as the competitor/generic will be able to be approved the day after the exclusivity has expired. According to the current regulation the generic could only be submitted ('accepted') from that day. This means that currently the approval time for generics prolongs the effective protection of the innovative product.

Market exclusivity effective length reduction

Current exclusivity

1. ...the Community and the Member States shall **not**, for a period of 10 years, **accept another application** for a marketing authorisation, or grant a marketing authorisation **or accept an application to extend an existing marketing authorisation**, **for the same therapeutic indication**, in respect of a similar medicinal product.

Legal basis: Art 8 Current Orphan Reg

Proposal

Article 71: Market exclusivity

1. Where an orphan marketing authorisation is granted and without prejudice to intellectual property law, the Union and the Member States shall **not grant a marketing authorisation or extend an existing marketing authorisation, for the same therapeutic indication**, in respect of a similar medicinal product for the duration of market exclusivity set out in paragraph 2.
- ...
6. The market exclusivity of the orphan medicinal product shall **not prevent the submission, validation and assessment** of an application for a marketing authorisation for a similar medicinal product, including generics and biosimilars, where the **remainder of the duration of the market exclusivity is less than two years**.

Effective protection will be significantly reduced as the competitor/generic will be able to be approved the day after the exclusivity has expired.

According to the current regulation the generic could only be submitted ('accepted') from that day. This means that currently the approval time for generics prolongs the effective protection of the innovative product.

Legal basis: Art 71 New Reg

Market exclusivity effective length reduction

Current exclusivity

1. ...the Community and the Member States shall not, for a period of **10 years**, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Article 13 New Dir:
Article 13: Applications based on bibliographic data

Legal basis: Art 8 Current Orphan Reg

Proposal

Article 71: Market exclusivity

...

2. The duration of market exclusivity shall be as follows:
 - (a) **nine years** for orphan medicinal products other than those referred to in points (b) and (c);
 - (b) **ten years** for orphan medicinal products addressing a **high unmet medical need** (HUMN) ...;
 - (c) **five years** for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].

Article 70: Orphan medicinal products addressing a high unmet medical need

1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:
 - (a) there is **no medicinal product authorised** in the Union for such condition **or** where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, **will bring exceptional therapeutic advancement**;
 - (b) the use of the orphan medicinal product results in a **meaningful reduction in disease morbidity or mortality for the relevant patient population**.

Legal basis: Art 71 New Reg

What is the [Orphan] market exclusivity for a known active substance not authorized based on bibliographic data?

The Explanatory Memorandum and Art 71(2) of New Reg seem not to be aligned:

According to article 71(2), a known active substance not authorized based on bibliographic data and not addressing a HUMN should have 9 years of market exclusivity.

However, according to the Explanatory Memorandum 9 years were intended for new active substances and it is unclear what exclusivity was intended for known active substance not authorized based on bibliographic data.

Article 71(2): Market exclusivity (New Reg)

The duration of market exclusivity shall be as follows:

- (a) **nine years** for orphan medicinal products other than those referred to in points (b) and (c);
- (b) **ten years** for orphan medicinal products addressing a **high unmet medical need** (HUMN) ...;
- (c) **five years** for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].

Article 13: Applications based on bibliographic data (New Dir)

In cases where no reference medicinal product is or has been authorised for the active substance of the medicinal product concerned, the applicant shall, by way of derogation from Article 6(2), **not be required to provide the results of non-clinical tests or clinical studies** if the applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Union for the same therapeutic use and route of administration and for at least **ten years**, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex II. In that event, the test and trial results shall be replaced by **appropriate bibliographic data** in the form of **scientific literature**.

Explanatory Memorandum of New Reg, page 12

Option C provides for a variable duration of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicinal product (for HUMN, **new active substances** and **well-established use** applications respectively). A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility in all relevant Member States, but only for HUMN products and **new active substances**.

Which are the 'five years' products?

Can an orphan indication be based on bibliographic studies? A marketed product that is used off-label for the orphan condition for more than ten years could potentially qualify to an application based on bibliographic data (it does not seem to be a likely situation).

However, maybe it would not have commercial sense as doctors could continue to use the original product off label and not buy the orphan medicine at a higher price.

In any case, what is the purpose of providing incentives for a product that is already used for the condition to a holder who has not carried out clinical trials?

Maybe the intention was to grant 5 years of market exclusivity for 'known active substances' in opposition to 'new active substances'. From the Explanatory Memorandum of New Reg, page 12:

Option C provides for a variable duration of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicinal product (for HUMN, **new active substances** and **well-established use** applications respectively). A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility in all relevant Member States, but only for HUMN products and **new active substances**. ...Option C was considered to be the best policy choice...

The Explanatory Memorandum and Art 71(2) of New Reg setting the 9 years period seem not to be aligned.

5 years of market exclusivity for 'known active substances' would clearly disincentivize the development of orphan medicinal products.

See also Explanatory Memorandum of New Reg, page 16:

The duration of market exclusivity is set at [nine] years, except for: (i) orphan medicinal products addressing HUMN, which will get [ten] years, and (ii) well-established use orphan medicinal products, which will be granted [five] years of market exclusivity. A 'bonus' market exclusivity extension of [one] year can be granted, based on patient access in all relevant Member States.

Market exclusivity for additional orphan indications

Current law

10 Y Indication 1

Active Substance A for Indication 1 holder H

10 Y Indication 2

Active Substance A for Indication 2 holder H

10 Y Indication 3

Active Substance A for Indication 3 holder H

Market exclusivity for all the Indication[s] of H

9 Y + 12 M + 12 M

Active Substance A for Indication 1 holder H

Active Substance A for Indication 2 holder H

Active Substance A for Indication 3 holder H
(see Art 72(2) New Reg)

Proposal

New concept of “Global Orphan Marketing Authorisation” (GOMA) providing a single period of orphan market exclusivity for each ‘molecule’ rather than the indication.

9 Y Indication 4

Active Substance A for Indication 4 holder **H2**

New orphan Indication 2
New orphan Indication 3

The orphan medicinal products which benefit from the prolongation of market exclusivity for new orphan indications shall not benefit from the additional period of data protection associated with new indications with significant clinical benefit
(see Art 72(3) New Reg)

New Indication significant clinical benefit

Market exclusivity for additional orphan indications

Current exclusivity

No limitation: Each new indication can be protected by an independent orphan market exclusivity.

Legal basis: Art 8 Current Orphan Reg

Proposal

Article 71: Market exclusivity

...

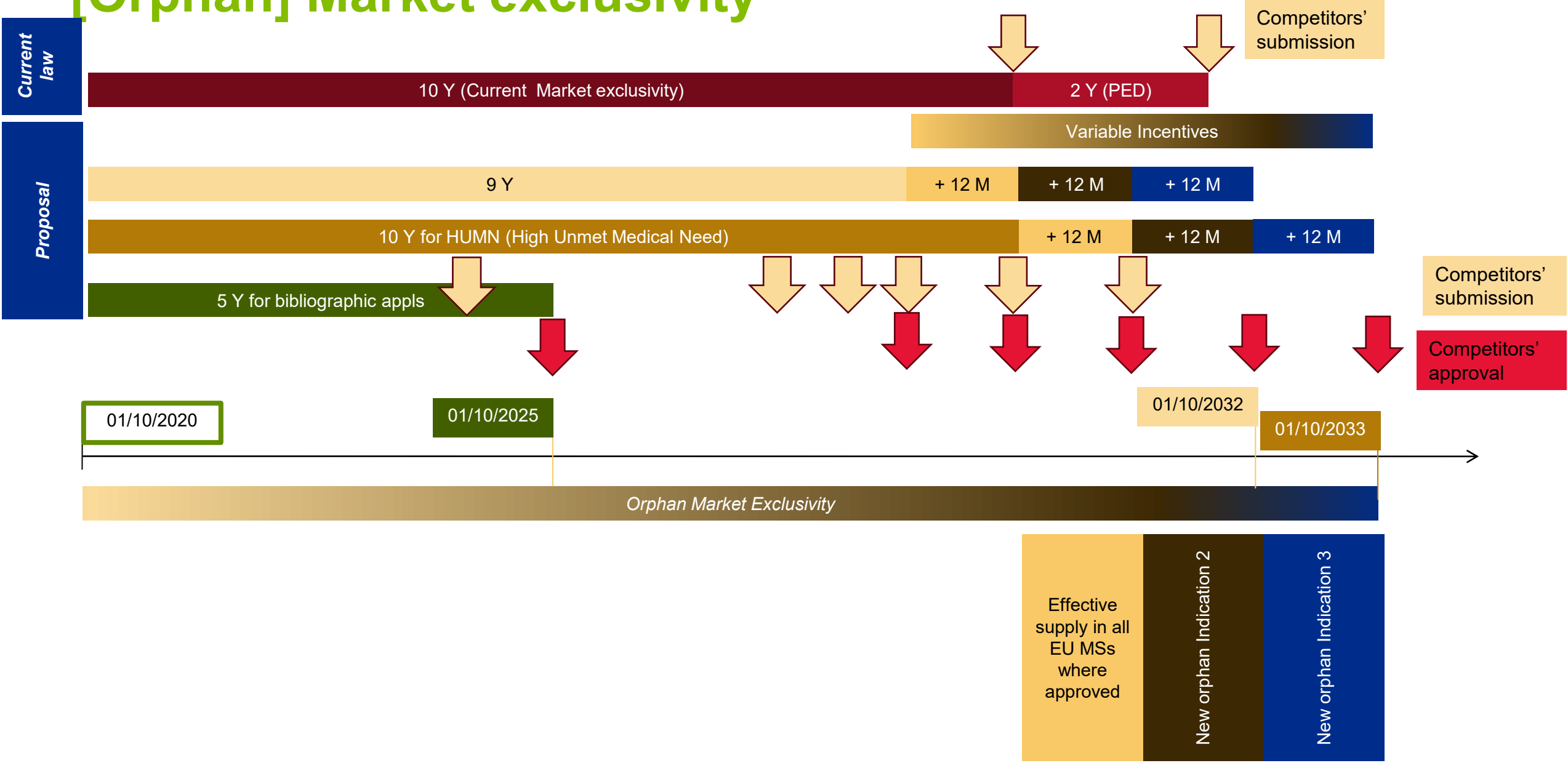
3. Where a marketing authorisation holder holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the Union.

It discriminates the first marketing authorisation holder against other parties. This could disincentivize the pursue of new orphan indications by the first holder.

By having additional orphan indications, the first marketing authorisation holder can extend market exclusivity by 12 months for each indication, with a maximum of two further indications.

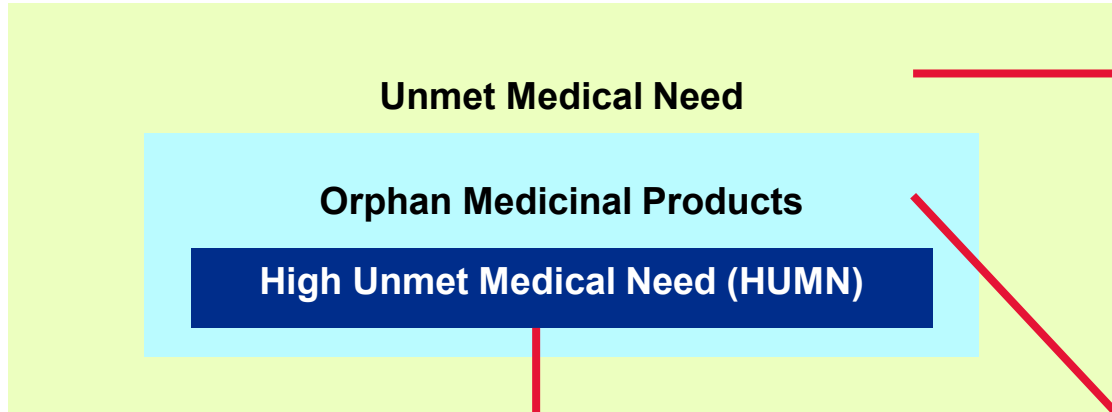
Legal basis: Art 71 and 72 New Reg

[Orphan] Market exclusivity



High Unmet Medical Need

Orphan medicines



At least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following is met:

- (a) no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised, the disease is associated with a remaining high morbidity or mortality;
- (b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population

OR meets orphan requirements

Either:
 no medicinal product authorised for the condition or if there is one, in addition to having a significant benefit, the product must bring exceptional therapeutic advancement.
 The use of the orphan medicinal product must result in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition

- (a) the condition affects not more than five in 10 000 persons in the Union ...;
- (b) no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, the medicinal product would be of significant benefit ...

[Alternative to a) possible upon proposal of the Commission]

(High) Unmet Medical Need: Feedback received

(High) Unmet Medical Need (HUMN)

EUCOPE acknowledges the need to steer investments toward underserved areas, but this should not be done on the basis of the strict and unpredictable concept of (high) unmet medical need ((H)UMN). Vague concepts such as ‘exceptional therapeutic advancement’ and ‘meaningful reduction in morbidity or mortality’ introduce more unpredictability and unclarity...

Labelling a product as not addressing (H)UMN will have significant P&R implications, inform investment decision whether to pursue R&D activities in certain disease areas and the commercial viability of a therapy, and it will ultimately jeopardise broader patient access. First-to-market therapies do not necessarily address the needs of the entire patient population living with a given disease. Modulation based on HUMN risks hampering innovation and overlooking the needs of diverse patient populations living with a rare disease.

Source:

[Feedback from: European Confederation of Pharmaceutical Entrepreneurs \(EUCOPE\) \(europa.eu\)](http://europa.eu)



Orphan medicinal products addressing a high unmet medical need (HUMN)

Article 70: Orphan medicinal products addressing a high unmet medical need

1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:
 - (a) there is **no medicinal product authorised** in the Union for such condition **or** where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, **will bring exceptional therapeutic advancement**;
 - (b) the use of the orphan medicinal product results in a **meaningful reduction in disease morbidity or mortality for the relevant patient population**.

Prolongation of [orphan] market exclusivity

Article 72: Prolongation of market exclusivity (New Reg)

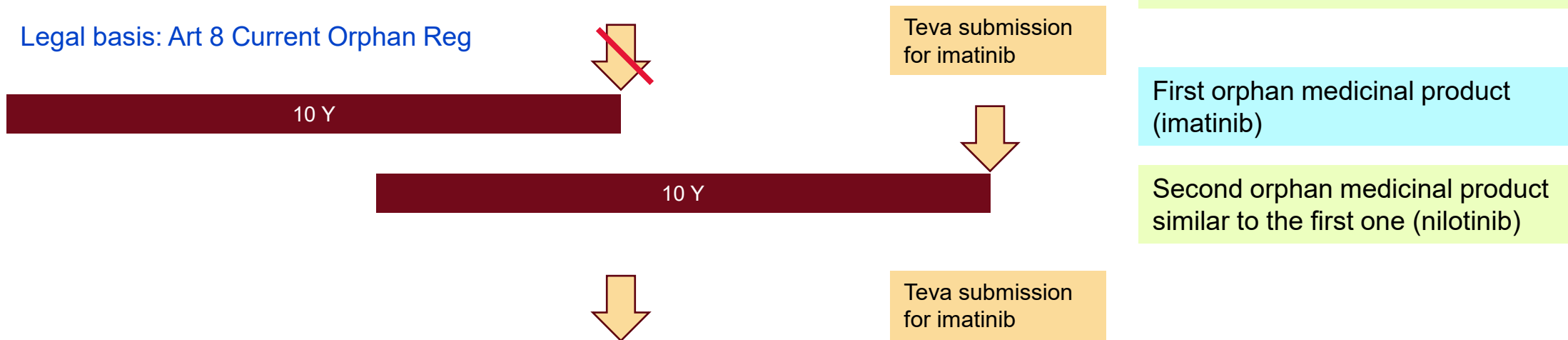
1. The periods of market exclusivity referred to in Article 71, paragraph 2, points (a) and (b), shall be prolonged by 12 months, where the orphan marketing authorisation holder can demonstrate that the conditions referred to in Article 81(2), point (a), and Article 82(1) [of revised Directive 2001/83/EC] are fulfilled.
The procedures set out in Articles 82(2) to (5) [of revised Directive 2001/83/EC] shall accordingly apply to the prolongation of market exclusivity.
2. The period of market exclusivity shall be prolonged by an additional 12 months for orphan medicinal products referred to in Article 71(2), points (a) and (b), if at least two years before the end of the exclusivity period, the orphan marketing authorisation holder obtains a marketing authorisation for one or more new therapeutic indications for a different orphan condition.
Such a prolongation may be granted twice, if the new therapeutic indications are each time for different orphan conditions.
3. The orphan medicinal products which benefit from the prolongation of market exclusivity referred to in the paragraph 2 shall not benefit from the additional period of data protection referred to in Article 81(2), point (d), of [revised Directive 2001/83/EC].
4. Article 71(3) equally applies to the prolongations of market exclusivity referred to in paragraphs 1 and 2.

Effective scope of market exclusivity

Current law

1. ...the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

Legal basis: Art 8 Current Orphan Reg



Proposal

Market exclusivity effective scope reduction

Current law

1. ...the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, **in respect of a similar medicinal product.**

Legal basis: Art 8 Current Orphan Reg

Proposal

Article 71: Market exclusivity

...

5. The **submission, validation and assessment** of the application for the marketing authorisation and granting the marketing authorisation for a generic or biosimilar product to the reference medicinal product **for which market exclusivity has expired**, shall **not be prevented by the market exclusivity of a similar product** to the reference medicinal product.

In cases wherein

- a first orphan medicinal product (for example, imatinib) is approved and
- a similar second orphan medicinal product (for example, nilotinib) is approved later, for the same indication

the exclusivity of the second product will not prevent the approval of a generic of the first product as happened in the case Teva imatinib, T-140/12 (General Court), appealed at the Court of Justice (C-138/15 P).

The abridged dossier of Teva for imatinib was not accepted because imatinib was a product similar to nilotinib, which had orphan market exclusivity for the same indication.

Legal basis: Art 71 New Reg

Market exclusivity

Article 71: Market exclusivity

1. Where an orphan marketing authorisation is granted and without prejudice to intellectual property law, the Union and the Member States shall not grant a marketing authorisation or extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product for the duration of market exclusivity set out in paragraph 2.
2. The duration of market exclusivity shall be as follows:
 - (a) nine years for orphan medicinal products other than those referred to in points (b) and (c);
 - (b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;
 - (c) five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].
3. Where a marketing authorisation holder holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the Union.

Art 71 New Reg

Market exclusivity

4. By way of derogation from paragraph 1, and without prejudice to intellectual property law, the marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:
 - (a) the marketing authorisation holder for the original orphan medicinal product has given consent to the second applicant, or
 - (b) the marketing authorisation holder for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
 - (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.
5. The submission, validation and assessment of the application for the marketing authorisation and granting the marketing authorisation for a generic or biosimilar product to the reference medicinal product for which market exclusivity has expired, shall not be prevented by the market exclusivity of a similar product to the reference medicinal product.
6. The market exclusivity of the orphan medicinal product shall not prevent the submission, validation and assessment of an application for a marketing authorisation for a similar medicinal product, including generics and biosimilars, where the remainder of the duration of the market exclusivity is less than two years.

Art 71 New Reg

05

Incentives for pediatric
medicines

Option preferred for paediatric medicines

In option C, like today, the 6-month SPC extension remains the main reward for completing a PIP. All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered the best policy choice, taking into account the proposed measures' specific objectives and economics and social impacts. Option C is expected to yield to an increased number of medicinal products, in particular in areas of unmet medical needs of children, which are expected to reach children faster than today. It would also ensure a fair return of investment for medicinal products developers who fulfil the legal obligation to study medicinal products in children, as well as reduced administrative costs linked to the procedures that follow from the obligation.

Page 13 of Explanatory Memorandum of New Reg, under 3. RESULTS OF EX-POST EVALUATIONS, STAKEHOLDER CONSULTATIONS AND IMPACT ASSESSMENTS; / Impact assessments / Orphan and paediatric legislation

Paediatric use marketing authorisations

Paediatric use marketing authorisation = PUMA

- (11) 'paediatric use marketing authorisation' means a marketing authorisation granted in respect of a medicinal product for human use which is
- not protected by a supplementary protection certificate ... or by a patent which qualifies for the granting of the supplementary protection certificate,
 - covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

Defined in Art 2(11) of New Reg



Incentives for pediatric medicines

Exclusivity	Current law	Proposal
<p>For conducting pediatric studies according to the Paediatric Investigational plan (PIP):</p> <ul style="list-style-type: none"> ▪ SPC pediatric extensions (6 months) ▪ Extension of 2 years of orphan market exclusivity ▪ SPC pediatric extension <u>also</u> for orphan medicinal products 	<p>✓ ✓ 2 ✗ 3</p>	<p>✓ 1 ✗ ✓</p>
<ul style="list-style-type: none"> ▪ Paediatric Use Marketing Authorisations (PUMAs) 	<p>Same exclusivities as for innovative drugs 8+2[+1]</p>	<p>Same exclusivities as for innovative drugs 6[+2][+1/2][+1/2][+1]+2 4</p>
<ul style="list-style-type: none"> ▪ Applicants <u>cannot</u> use paediatric studies at the same time for: <ul style="list-style-type: none"> ▪ SPC extension and ▪ one-year extension of the period of regulatory data protection*, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies 	<p>✓</p> <p style="writing-mode: vertical-rl; transform: rotate(180deg);">New indication significant clinical benefit</p>	<p>✓ 1</p>

Legal bases: 1) Art 86 New Dir; 2) Art 37 Ped Reg (Reg (EC) No 1901/2006); 3) Art 36(4) Ped Reg; 4) Art 93 New Reg

* 'marketing protection' is wrongly mentioned in Art 86 New Dir. It should state 'regulatory data protection' in my view.



2 year extension of [orphan] market exclusivity and PUMAs rarely used

The other major rewards provided by the Regulation, **the additional two years of market exclusivity (the 'orphan reward') and the paediatric use marketing authorisation, PUMA, have rarely been used.** They have thus done little to boost development in areas of unmet paediatric needs. The orphan reward, which cannot be granted in addition to the six-month extension of the SPC, is considered less valuable by developers than the SPC extension. Consequently, developers prefer to seek an SPC extension whenever possible*.

The PUMA scheme, designed to channel EU research funds into boosting the development of new paediatric indications in off-patent medicines, has yielded disappointing results so far. However, **about 20 PUMA-related PIPs are currently under way,** so outcomes may improve in the next few years. Factors beyond the Regulation are the main reasons for the PUMA scheme's failure to yield more than a limited number of products. One example is the **difficulty of obtaining higher prices than those applicable to the existing product,** to cover the cost of new clinical research. Another is the difficulty encountered in conducting paediatric clinical trials of old products that are already available on the market and often widely used off-label.

Under 'Conclusions', on page 106; Brussels, 11.8.2020, SWD(2020) 163 final, PART 1/6, COMMISSION STAFF WORKING DOCUMENT; EVALUATION;

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

*Comment: in case of an orphan medicinal product there was no choice possible, the only reward available was the extension of orphan market exclusivity.

06

New vouchers for priority antimicrobials addressing antimicrobial resistance

What is a 'priority antimicrobial'?

An antimicrobial shall be considered as 'priority antimicrobial' if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and meets one of:

- (a) it represents a new class of antimicrobials;
- (b) its mechanism of action is distinctly different from that of any authorised antimicrobial in the Union;
- (c) it contains an active substance not previously authorised in the Union that addresses a multi-drug resistant organism and serious or life threatening infection.



Legal basis: Art 40(3) New Reg
'underpin' ~ 'support'

Vouchers for priority antimicrobials

- Voucher = additional 12 months of data protection for one authorised medicinal product
- Granted by the Commission when a holder applies for a marketing authorisation of a 'priority antimicrobial' if the scientific assessment by the EMA is positive
- Transferable to other products and/or holders
- Use of the voucher:
 - only once,
 - for a single centrally authorised medicinal product and
 - only within the first four years of regulatory data protection
 - marketing authorisation of the priority antimicrobial not withdrawn
 - to use the voucher, its owner shall apply for a variation to extend the data protection



Legal basis: Chapter III, Incentives for the development of 'priority antimicrobials', Arts 40-43, New Reg

Vouchers for priority antimicrobials

- The voucher
 - expires within 5 years from the date of grant
 - can be revoked prior to its transfer if a request for supply, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled
- Limited incentive
 - 15 years from entry into force of New Reg
 - Maximum of 10 vouchers granted



Legal basis: Chapter III, Incentives for the development of 'priority antimicrobials', Arts 40-43, New Reg

Thank for your attention

Thanks to Ferrer's Patent Team for comments and ideas.
Opinions expressed are those of the author only and may not represent the stance of Ferrer.