# European Paediatric Cancer Community Proposal for Improvement of the EU Revised Pharmaceutical Legislation

## INTRODUCTION AND BACKGROUND

The **European Society for Paediatric Oncology (SIOPE),** the single-united European organisation representing all healthcare professionals in paediatric oncology, and **Childhood Cancer International – Europe (CCI-E)**, the largest European patient' organisation in paediatric cancer, have been involved in the review and analysis process of the EU Paediatric Regulation since 2012 and the EU Orphan Regulation since 2016.

**We warmly welcome the EU Commission's revised Pharmaceutical legislation**, as stated in our joint statement available here. We believe it addresses several areas of concern of the paediatric cancer community.

Today, neither the EU Paediatric nor the EU Orphan Regulations have succeeded in significantly improving young cancer patients' chance of survival. Notably, over the last ten years, only 16 anticancer medicines have been authorised for a specific paediatric cancer indication, in contrast to over 150 for adult cancers[1]. Now, we are calling for an ambitious revision that will support and accelerate innovation and put the unmet medical needs of patients and their families at the centre of a European strategy for medicine development.

Therefore, SIOPE and CCI-E have identified **six key priority areas** which require focused consideration during the negotiation of the revised EU Pharmaceutical legislation. We have **detailed below areas which should be upheld, as well as areas with specific suggestions for amendments** which can further strengthen the reform and ultimately, improve the outcomes of patients with unmet medical needs such as young cancer patients and restore them to their full health.

Attached to this document is an annex listing the articles of the revised EU Pharmaceutical legislation that we propose to maintain, as well as the amendments that we advocate.

## PRIORITY AREAS FOR PAEDIATRIC CANCER COMMUNITY

### 1. Unmet Medical Needs (UMN) and High Unmet Medical Needs (high UMN)

We welcome the introduction of important concepts of UMN and high UMN in the proposal for revision of the EU Pharmaceutical legislation.

In the field of paediatric cancer, off-label use of anti-cancer medicine is very common due to lack of specific paediatric cancer drugs. This leads to a vast amount of side effects of currently available treatments.

> "*The onset of these side effects can be acute or chronic, having the potential to result in a severe disabling, life-threatening or fatal illness, such as a cardiovascular disease, stroke, pulmonary fibrosis, kidney failure, or even a second malignancy […] Novel interventions aimed at reducing acute side effects, as well as the long-term burden on survivors who are at most risk from treatment related side effects, are also required*"[2].

[1] Vassal et al., "Impact of the EU Paediatric Medicine Regulation on New Anticancer Medicines for the Treatment of Children and Adolescents, The Lancet Child & Adolescent Health, 2023 (https://www.thelancet.com/pdfs/journals/lanchi/PIIS2352-4642(22)00344-3.pdf).

[2] Skinner, R., Ruggiero, A., Khaled Zekri, W. Z., eds, "Adverse and Toxic Effects of Childhood Cancer Treatments", Lausanne: Frontiers Media SA, 2021 (https://www.frontiersin.org/research-topics/15170/adverse-and-toxic-effects-of-childhood-cancer-treatments).

We argue that investment in novel medicines overall reduces the financial burden of governments. New drugs that bear lower toxicity levels would reduce long term side effects of paediatric cancer patients and enable them to be productive members of society later in life. This would overall reduce the financial burden of governments as the savings in social security spendings for patients affected by long-term side effects outweigh the spendings for innovative drug development.

> "*For several illnesses, costs due to productivity losses are higher than the direct medical costs. From a societal perspective and according to the World Health Organization (WHO), an unhealthy population unable to work will reinforce labor shortages and affect fiscal budgets*"[3].

Furthermore, today's standards of care involve acute toxicity, which impacts both the young patient and his or her parents. For the young patient, acute toxic prevents him or her to attend school and to develop social skills that his or her peers acquire at the same age. This time lost cannot be simply gained back upon their return in school, which implies that their educational track is in average more complex than that of their peers.

For his or her parents, this acute toxicity implies that with their child confined at home or in hospital, one of them cannot meaningfully pursue his or her career in order to care for their child and attend to his or her needs. As a result, a child's acute disease also has an indirect impact on the economy and the financial prospect of the parents.

- ➢ Therefore, we believe the conditions provided for in Article 83 of the Directive and Article 70 of the Regulation should allow a medicinal product to be considered as addressing a UMN or high UMN when it reduces acute or long-term toxicity.

In addition, we advocate the creation of a flexible regulatory framework to define both concepts through a multistakeholder discussion process involving academia and reflecting patients' needs.

- ➢ Article 162 of the Regulation should therefore provide for patient and healthcare professional organisations such as CCI-E and SIOPE to be systematically included in the consultation process when developing guidelines on UMN or high UMN with the EMA, the Commission, national authorities or other bodies.

## 2. Science based Paediatric Medicine Development

We welcome the introduction of paediatric medicine development based on the molecular target of a new medicine in the proposal for a Regulation. Indeed, under the current framework, there is no obligation for a medicine developer to submit a Paediatric Investigation Plan (PIP) if the medicine originally developed for an adult cancer does not exist in children, even when the medicine has a relevant mechanism of action for a given type of paediatric cancer from a biological/molecular perspective.

In addition, the use of the concept of molecular target is aligned with the US RACE for Children Act and meets our expectation to harmonise the global regulatory environment in the field of drug development in paediatric oncology.

- ➢ We therefore recommend that Article 75 of the Regulation be upheld and voted as drafted in the proposal.

[3] Claudio Schiener, C., Manuel Störzel, M., Jason Maro, J., Prof. Dr. Ostwald, D., "Social Impact of innovative medicines – a systematic approach to capture the societal and macroeconomic dimension of medicines", WifOR Berlin: A Meta Study for Novartis, 2021 (https://www.wifor.com/uploads/2021/12/Social_Impact_of_Innovative_Medicines-3.pdf).

### 3. Early Start of the Paediatric Development

We commend the introduction of the stepwise Paediatric Investigation Plan (PIP) which aims to accelerate and simplify paediatric medicine development, foster evidence generation to inform life cycle PIP considerations, and support developments based on needs and robust science.

- ➢ However, we recommend that Article 76 of the Regulation stipulates a clear obligation to submit PIPs upon completion of phase I of clinical studies in adults rather than prior to the initiation of the phase II clinical studies in adults. In addition, penalties to deter companies from delaying the submission of the PIP should be introduced.

Furthermore, we support the cap applied to the PIP deferral to the extent that the total duration of the deferral may not exceed 5 years.

- ➢ Article 82 of the Regulation should be amended to set a limit on the time to respond to requests for supplementary information, which suspend the 60-days decision period granted to the Agency.

### 4. Academic Repurposing

We support the proposal to facilitate the repositioning of medicines, shelved or developed for other conditions, for the treatment of paediatric diseases. We also support the envisioned role of non-for-profit entities (academia) in generating data for repurposed medicines through fit-for-filing (a dataset that meets the expectations for inclusion in a regulatory package) trials. Furthermore, we appreciate the 4 years of extra data protection granted to repurposed medicinal products for the authorisation of a new indication.

- ➢ We therefore recommend that Article 48 of the Regulation and Article 84 of the Directive be upheld and voted as drafted in the proposal.

This measure will require adequate resources for academic-led research and increased capacity within the EMA to improve access without delay to lifesaving medicines for patients who must otherwise resort to medicines prescribed off-label. Furthermore, to that end, we believe a mechanism will be necessary to ensure that industry provides academia with novel medicines and funding for the trials.

### 5. Improved Access to Novel and Essential Anticancer Medicines

Children with cancer across Europe experience inequalities in access to the best available standard diagnostics, treatment, care and research protocols. These disparities contribute to differences in survival of 20% or more and are of greater concern in particular eastern European countries than those in northern and western Europe.[4]

We therefore welcome the European Commission's proposal to strengthen incentives for a swifter launch and earlier access medicines for patients.

#### *5.1. Novel Medicines*

Currently, newly approved medicines are not introduced into clinical practice in all Member States. We are pleased that the European Commission is willing to address the issue of equal access to medicines for children with cancer in the European Union with a dedicated incentive.

[4] Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol. 2014;15(1):35–47 (http://www.ncbi.nlm.nih.gov/pubmed/24314616).

- ➢ We therefore recommend that articles 59, 81 and 82 of the Directive be upheld and voted as drafted in the proposal.

*5.2. Essential Medicines*

We are delighted to see a dedicated chapter on the shortages of medicine and the long-awaited Union List of Critical Medicinal Products, and we are eager to collaborate on the implementation of these important initiatives. We expect, as patient and healthcare professional organisations, to be included in the consultation process for establishing this list to ensure essential medicines for children with cancer are incorporated.

- ➢ We therefore are delighted about Chapter X in the Regulation, especially highlighting Article 131 of the Regulation, and recommend upholding the provisions as drafted in the proposal.

**6. First-in-Child Innovation**

The current proposal does not include specific incentives for first-in-child development and first-in-child marketing authorisation of medicines.

The complexities associated with paediatric cancer and the small patient population have resulted in the development of paediatric anticancer drugs being overlooked. Indeed, the various challenges in designing clinical trials in children, such as the need to centralise clinical trials in a limited number of centres and the difficulty of recruiting patient as well as the heterogeneity of the paediatric population in need of age-specific formulations are all factors that contribute to make investments in the development of drugs for a small, high-risk population economically unattractive for pharmaceutical companies.

Therefore, we strongly recommend including a first-in-child marketing authorisation incentive, as this would be expected to increase commercial interest in the development of medicines specific to paediatric cancers (and paediatric rare diseases).

- ➢ We advocate the introduction of a new 12-year period of market exclusivity in Article 71 of the Regulation for orphan medicinal products whose first authorised indication addresses a high UMN in a paediatric population.

Besides, we call for programmes allocating public funds to research projects addressing Unmet Medical Needs in paediatric indications.

**ABOUT EUROPEAN CHILDHOOD CANCER ORGANISATIONS**

**Childhood Cancer International - Europe (CCI-E, or CCI Europe)** represents childhood cancer parent and survivor groups as well as other childhood cancer organisations in Europe: 67 organisations in 34 European countries are members of CCI-E. CCI Europe works together with all relevant stakeholders for the same aim: help children and adolescents with cancer to be cured, with no - or as few as possible - long term health problems/late effects. **(www.ccieurope.eu)**

**The European Society for Paediatric Oncology (SIOPE, or SIOP Europe)** is the single united European organisation representing all professionals working in the field of childhood cancers. With more than 2,500 members across 35 countries, SIOP Europe is leading the way to ensure the best possible care and outcomes for all children and adolescents with cancer in Europe. **(www.siope.eu)**

## ANNEX: SUGGESTED AMENDMENTS & CONTINUATIONS

Please find below the SIOPE and CCI-E detailed priority areas, listing the articles that shall be amended or upheld. Highlighted in **gold are the amendments** that we would like to see in the final legislation, and in **green the wording that we would like to see upheld** in the final legislation.

| **Articles in the proposal for revision of the EU Pharmaceutical legislation of the EU Commission** | **Suggested Amendments/Continuations from SIOPE & CCI-E** |
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| **PRIORITY 1. Unmet Medical Needs (UMN) and High Unmet Medical Needs (high UMN)** | |
| **Directive Article 81. Regulatory data protection periods** | |
| (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(...)<br><br>(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;<br><br>(...) | (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(...)<br><br>(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;**<br><br>(...) |
| **Directive Article 83. 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:<br><br>(a) there is no medicinal product authorised in the Union for such disease, or, where | 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:<br><br>(a) there is no medicinal product authorised in the Union for such disease, or, where |

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| despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;<br><br>(b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.<br><br>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.<br><br>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]. | despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;<br><br>(b) the use of the medicinal product results in a meaningful reduction in disease morbidity, **acute or long-term toxicity** or mortality for the relevant patient population.<br><br>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.<br><br>3. Where the Agency adopts scientific guidelines for the application of this Article it shall consult the Commission and the authorities or bodies **as well as the stakeholders** referred to in Article 162 of [revised Regulation (EC) No 726/2004]. |
| **Regulation 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:<br><br>(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;<br><br>(b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.<br><br>2. A medicinal product for which an application has been submitted in accordance with Article 13 of [revised Directive 2001/83/EC] shall not be considered as addressing a high unmet medical need.<br><br>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. | 1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:<br><br>(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;<br><br>(b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity, **acute or long-term toxicity** or mortality for the relevant patient population.<br><br>2. A medicinal product for which an application has been submitted in accordance with Article 13 of [revised Directive 2001/83/EC] shall not be considered as addressing a high unmet medical need.<br><br>3. Where the Agency adopts scientific guidelines for the application of this Article, it shall consult the Commission, the authorities or bodies **as well as the** |

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| | **stakeholders** referred to in Article 162. |
| **Regulation Article 162. Consultation process** | |
| (...)<br><br>2. The Agency may extend the consultation process to patients, medicine developers, healthcare professionals, industries or other stakeholders, as relevant. | (...)<br><br>2. The Agency **shall** extend the consultation process to patients, medicine developers, healthcare professionals, industries or other stakeholders, as relevant. |
| **PRIORITY 2. Science based paediatric medicine development** | |
| **Regulation Article 75. Waivers** | |
| 1. In accordance with the procedure set out in Article 78, the Agency may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:<br><br>(a) (…)<br><br>(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, unless when the product is directed at a molecular target that on the basis of existing scientific data, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population;<br><br>(...) | 1. In accordance with the procedure set out in Article 78, the Agency may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:<br><br>(a) (…)<br><br>(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, **unless when the product is directed at a molecular target that on the basis of existing scientific data, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population**;<br><br>(...) |
| **PRIORITY 3. Early start of the paediatric development** | |
| **Directive Article 81. Regulatory data protection periods** | |

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| (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(...)<br><br>(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.<br><br>(...) | (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(...)<br><br>(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.**<br><br>(...) |
| **Directive Article 86. Rewards for paediatric medicinal products** | |
| 1. Where an application for marketing authorisation, includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Article 13, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].<br><br>The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.<br><br>(...)<br><br>4. In the case of an application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of | 1. **Where an application for marketing authorisation, includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Article 13, paragraphs 1 and 2 of** [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].<br><br>**The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication**, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.<br><br>(...)<br><br>4. In the case of an application for new therapeutic indications, including paediatric |

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| administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, **a** one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 81(2), first subparagraph, point (d). | indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, **a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 81(2), first subparagraph, point (d).** |
| **Regulation Article 76. Validation of a paediatric investigation plan or of a waiver** | |
| 1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency with a request for agreement, except in duly justified cases, before the initiation of safety and efficacy clinical studies so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned.<br><br>2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.<br><br>3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.<br><br>4. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article. | 1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency with a request for agreement **upon completion of the human pharmaco-kinetic studies in adults specified [in Section 5.2.3. of Part I of Annex I to Directive 2001/83/EC]**, except in duly justified cases, so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned.<br><br>2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.<br><br>3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.<br><br>4. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.<br><br>**5. At the Agency's request, the Commission may impose financial penalties on the** |

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| | **applicants under this Regulation if they fail to submit a paediatric investigation plan or an application for waiver in the provided time frame. The maximum amounts as well as the conditions and methods for collection of these penalties shall be laid down in accordance with the procedure referred to in Regulation (EC) No 658/2007.** |
| **Regulation Article 82. Prolongation of deferrals** | |
| 1. In duly justified cases, a request for a prolongation of the deferral, may be submitted, at least 6 months before the expiry of the deferral period. A prolongation of the derogation shall not exceed the duration of the deferral period given under Article 81(3).<br><br>The Agency shall decide on the prolongation within 60 days.<br><br>2. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 60 days shall be suspended until the supplementary information requested has been provided.<br><br>3. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency. | 1. In duly justified cases, a request for a prolongation of the deferral, may be submitted, at least 6 months before the expiry of the deferral period. A prolongation of the derogation shall not exceed the duration of the deferral period given under Article 81(3).<br><br>The Agency shall decide on the prolongation within 60 days.<br><br>2. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 60 days shall be suspended until the supplementary information requested has been provided. **The applicant must provide the supplementary information within 60 days.**<br><br>3. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency. |
| **PRIORITY 4. Academic Repurposing** | |
| **Regulation Article 48. Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products** | |
| 1. An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need.<br><br>The Agency may, at the request of a Member State, the Commission, or on its own | 1. An entity not engaged in an economic activity **('not-for-profit entity')** may submit to the Agency or to a competent authority of the Member State substantive non-clinical or **clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need.**<br><br>The Agency may, at the request of a Member State, the Commission, or on its own |

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| initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need.<br><br>The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.<br><br>2. In cases where the opinion is favourable, marketing authorisation holders of the medicinal products concerned shall submit a variation to update the product information with the new therapeutic indication. | initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need.<br><br>The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.<br><br>2. In cases where the opinion is favourable, marketing authorisation holders of the medicinal products concerned **shall** submit a variation to update the product information with the new therapeutic indication. |
| **Directive Article 84. 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:<br><br>(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<br><br>(b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefited from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.<br><br>(...) | 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:<br><br>(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<br><br>(b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefited from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.<br><br>(...) |

| PRIORITY 5. Improved Access to Novel and Essential Anticancer Medicines | |
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| **Directive Article 81. Regulatory data protection periods** | |
| (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(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:<br><br>(i) SMEs within the meaning of Commission Recommendation 2003/361/EC;<br><br>(ii) entities not engaged in an economic activity ('not-for-profit entity'); and<br><br>(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<br><br>(...) | (...)<br><br>2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:<br><br>(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:<br><br>(i) SMEs within the meaning of Commission Recommendation 2003/361/EC;<br><br>(ii) entities not engaged in an economic activity ('not-for-profit entity'); and<br><br>(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<br><br>(...) |

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| **Directive Article 82. Prolongation of the data protection period for medicinal products supplied in Member State** | |
| 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. | **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.** |
| **Directive Article 59. Placing on the market of products with paediatric indications** | |
| Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those medicinal products have already been marketed with other therapeutic indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the medicinal product on the market taking into account the paediatric indication in all Member States where the medicinal product is already placed on the market.<br><br>A register, coordinated by the Agency, and made publicly available, shall mention these deadlines. | Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those medicinal products have already been marketed with other therapeutic indications, the marketing authorisation holder **shall**, within two years of the date on which the paediatric indication is authorised, **place the medicinal product on the market taking into account the paediatric indication in all Member States where the medicinal product is already placed on the market.**<br><br>A register, coordinated by the Agency, and made publicly available, shall mention these deadlines. |
| **Regulation Article 131. The Union List of Critical Medicinal Products** | |
| 1. Following the reporting referred to in Article 130, paragraph 2, second subparagraph, and Article 130(5), the MSSG shall consult the working party referred to in Article 121(1), point (c). Based on this consultation, the MSSG shall propose a Union list of critical medicinal products authorised to be placed on the market of a Member State EN 120 EN pursuant to Article 5 of [revised Directive 2001/83/EC] and for which coordinated Union level action is necessary ("the Union list of critical | 1. Following the reporting referred to in Article 130, paragraph 2, second subparagraph, and Article 130(5), the MSSG shall consult the working party referred to in Article 121(1), point (c). Based on this consultation, the MSSG **shall propose a Union list of critical medicinal products** authorised to be placed on the market of a Member State EN 120 EN pursuant to Article 5 of [revised Directive 2001/83/EC] and for which coordinated Union level action is necessary ("the Union |

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| medicinal products”).<br><br>(...) | list of critical medicinal products”).<br><br>(...) |
| **PRIORITY 6. First-in-Child Innovation** | |
| **Regulation Article 71. Market exclusivity** | |
| (...)<br><br>2. The duration of market exclusivity shall be as follows:<br><br>(a) nine years for orphan medicinal products other than those referred to in points (b) and (c);<br><br>(b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;<br><br>(c) five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC] | (...)<br><br>2. The duration of market exclusivity shall be as follows:<br><br>(a) nine years for orphan medicinal products other than those referred to in points (b)**, (c) and (d);**<br><br>(b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;<br><br>**(c) twelve years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70 in the paediatric population;**<br><br>**(d)** five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC]. |