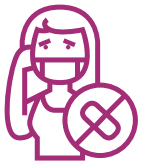
Affordable innovation for today's health issues through repurposing (value added medicines)

Thanks to the numerous medicines available today, we have made significant advancements in disease treatment and patient care. However, there is room to improve many of these treatments, and there are many new technologies that could enable this. These improvements stem from the experiences of patients who seek more effective treatments, doctors who constantly seek better options for their patients, pharmacists and nurses who witness firsthand the limitations of current medications and academics, NGOs and pharmaceutical companies committed to advancing healthcare.

By incorporating the collective wisdom and expertise from these diverse perspectives, we can revolutionise existing medicines and ultimately provide better health outcomes for individuals in need. Value Added Medicines aim to do this.



Address historic gender data gaps causing **women** to experience **60% more adverse reactions than men**[1].

For example, **zolpidem**, a commonly used medicine for insomnia, required nearly 20 years and thousands of pharmacovigilance reports to discover that the **appropriate dose for women is ½ of the dose for men**[2].

Optimise treatments against antimicrobial resistant bacteria which contributed to 4.95 million deaths worldwide in 2019[3].

Changing the route of administration can help reduce toxicity and ensure patients can complete their treatment, with for example, **inhalable formulations of antibiotics to treat pulmonary infections** (e.g. for cystic fibrosis patients or for infections with non-TB mycobacteria).

Reduce the pressure on healthcare professionals, already in short supply.

In England alone, **moving to ready-to-administer formulations** would save the equivalent of **4,000 nurses and free up 1 million hospital beds a year**[4]. Technological solutions can significantly reduce the burden on healthcare professionals and help direct their efforts to patient care, where they are needed the most.

Create **better health outcomes for 50% of patients** who struggle with adherence to treatment[5].

Improving adherence to treatment by using a fixed-dose combination for hypertension has led to a **30% reduction in death and cardiovascular events** for patients in Italy, while also r**educing the overall healthcare costs by 18%**[6].

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The research and development required for this is limited by a market failure of the current system. The lack of a dedicated framework which can recognise improvements made in the off-patent space prevents numerous solutions, such as the ones above, from being developed.

Addressing all these challenges in an affordable manner is within reach. Through the revision of the EU pharmaceutical legislation, there is a unique opportunity to correct this market failure and create a more sustainable ecosystem for affordable innovation.

The most important provision, that addresses these types of products is **Article 84 of the proposed Directive 2023/0132**. In essence, it ***introduces a reward of 4 years of data protection for new data which supports a new indication in an older, established product, if this brings significant benefit to patients. This proposal should cover all key technologies to support affordable innovation***.

For this, the following needs to be included in the legislation:

1. INCLUDE ALL MEANINGFUL BENEFITS

Why should Article 84 cover a wider range of technological improvements?

As illustrated in the healthcare examples above, there are **numerous changes required to significantly adapt existing medicines to tackle today's health issues**. **These improvements go well** beyond new indications (see Fig. 1) and include **changes in posology, pharmaceutical form, route of administration or type of device used**. If a reward of 4 years of data protection is limited to new indications only, many important affordable innovations will simply not be developed

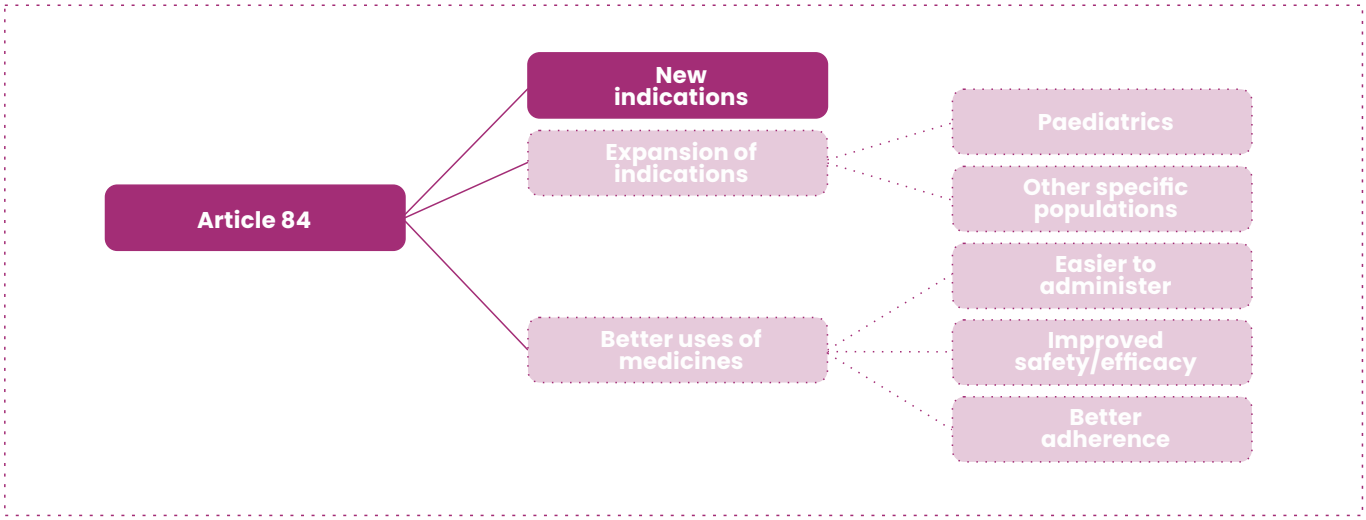

Fig. 1 Improvements currently excluded from the proposed Art 84

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Example: Improvements in oncology

- A reformulation of a **medicine used to treat leukaemia, which enabled effective treatment for an additional 20% of patients**[7], that were not receptive to this life-saving treatment with the original medicine.
- An improved version of a **medicine used to treat breast, pancreatic and lung cancer improved its efficacy by 50%.**

These changes do not result in new indications, however they bring life-saving improvements in oncology treatments.

Why should the legislation refer to significant benefit rather than significant clinical benefit?

Significant benefit is an established concept in the evaluation of medicines which encompasses clinical and patient centred benefits, such as improvements in adherence, patient quality of life or easier access to treatment (such as homecare versus hospital administration)[10] .

Aligning with this **concept maintains the magnitude of the benefit offered**, while ensuring a **patient-centred approach can be included in its evaluation**.

- **Example: Ready to use antimicrobials**. A ready to use formulation of a 30-yearold antibiotic which can be stored at room temperature ensures **easier and faster access to treatment**, which is particularly important in a life-threatening disease such as sepsis, where early intervention is critical to survival [11].
- Ready to use antimicrobials also **reduce burden on patients, who travel to hospital solely to receive intravenous treatment**[12] , as well as in ICU settings, **lowering microbiological contamination**[13].

While not a clinical benefit, moving care closer to home brings a significant benefit to patients' daily lives, particularly impacting those in remote and rural areas, where the closest hospital can be hours away. This is a well-documented challenge across most EU member state healthcare systems.

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2. ENSURE BALANCED INCENTIVES

Why are 4 years of data protection needed for affordable innovation?

As is the case for new molecules, **value added medicines developers must demonstrate the significant benefit of their innovation** compared to the existing generic version of the medicine. This requires a **significant investment in research** and drug development and reformulation. Since this innovation is less costly than a new molecule, a **shorter period of protection** is proposed (**4 years instead of the 11-12 years for new molecules**). Without this protection, there would be limited potential for the Value Added Medicine manufacturers to recoup their investment.

The **4 year duration is critical** because it provides manufacturers of the value added medicine with enough time to recover their investment. The EU legislation estimates that **manufacturers need around 2-3 years to market their medicines across the whole of Europe**[14] due to requirements to negotiate prices with different national reimbursement authorities. This would leave value added medicine manufacturers with **roughly 2 years of protection** after the full launch of the medicine.

According to the **European Commission's Impact Assessment** report for the revision of the general pharmaceutical legislation[15], **the time to patient access varies significantly between countries**, for example in one country the process takes less than **6 months,** while in others it can take **more than 2 years**, with a majority falling in between. Based on feedback from Medicines for Europe members, in reality for value added medicines, processes take even longer, due to the uncertainty caused by the lack of a dedicated pathway.

Reducing the protection to less than 4 years of data protection would therefore nullify the impact of any incentive coming from this provision in the legislation.

Will the data protection lead to unaffordable prices for healthcare systems?

No. Clearly, a value added medicines manufacturer needs some protection to recoup investment. However, **this protection will not lead to the withdrawal of the other generic medicines available on the market** which contain the same active ingredients. **This will give reimbursement authorities the option of reimbursing the value added medicine, the older generic medicine or a combination of the two.** As in the oncology example mentioned above, 20% of leukaemia patients require the VAM version; the other 80% could continue using the generic version.

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Yet, it is important for the **EU to learn the lessons from the experience with off-patent paediatric medicine developments**. PUMA products, **which benefit from 10 years of market exclusivity (as opposed to 4 years of data protection for Value Added Medicines)**, were rewarded through moderate increases in comparison to existing products. In other cases, however, the reimbursement price was too low to cover production costs, forcing manufacturers to withdraw children's medicines from the market. Consequently, only 9 PUMA medicines have been approved as of November 2023[16].

To remedy this issue, it would make sense for member states to recognise value added medicines, approved according to the new EU legislation, in their pricing and reimbursement systems.

This can be done in a sustainable way for both the healthcare system and the company, leading to a **neutral budget impact as this French example for paediatric off patent medicine shows:**

Example: French reimbursement rule on specific advantages for paediatric products[17]

In France, once a paediatric product is included in the **inventory of paediatric needs established by the EMA**, the manufacturer is guaranteed a **daily treatment cost equal to the daily treatment cost of the medicine in adults**. This ensures that, for example, a lower dose paediatric medicine is rewarded at least as much as the adult higher dose version.

This shows that a simple rule at Member State level can reward investment in the development of off-patent innovation (in this case for paediatric products), ensuring access to patients and sustainability for both the healthcare system and manufacturer.

Article 84 data protection vs other exclusivities

While both **data protection** and **market exclusivity** are a form of protection, they operate on different grounds. **Data protection** focuses on protection of data, ensuring that **other companies cannot rely on that data for their own regulatory submissions for a version of the same medicine. Market exclusivity,** on the other hand, grants exclusivity in terms of marketing and sales, providing companies with a defined timeframe during which they have the **sole rights to market and profit from the medicine**.

The **data protection in Article 84 only protects the new data generated by the company, not previously generated data, or any data in the public space. At the same time, generics or biosimilars of the original reference product remain on the market or other new versions could be introduced on the market**.

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Moreover, since the proposal is limited to data protection, and not market exclusivity, **other pharmaceutical companies would have the option to develop and market their own VAMs during the 4 year period** provided they conduct their own studies to support their application.

Therefore, article 84 should not be confused with the orphan exclusivity which prevents other companies from entering the market and can require the withdrawal of existing generic medicines.

Existing NCE exclusivity	Existing orphan exclusivities	Existing PUMA exclusivity	Proposed Article 84 exclusivity
10 years (data and market) for **full product**	10 y market exclusivity for **orphan indication**	10 years (data and market) for **new data**	4 years data protection for **new data**
Only new molecules	Both new and established molecules	Only established molecules	Only established molecules
No generic/biosimilar competition	Can force withdrawal of generics/biosimilars	No generic/biosimilar competition for paediatric indication.	Competition possible if company conducts their own studies.

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