Position Paper

Incentives Review
The Orphan and Paediatric Incentives

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Executive Summary

The European Union is conducting a review of the existing pharmaceutical incentives to innovation, following a request by Health Ministers in their Council Conclusions of June 2016, in order to tackle the strong pressure on healthcare budgets caused by the introduction of high-cost innovative products. Independent studies published by the European Commission and the Dutch Government have shown that while the incentives have been largely used and are to be considered rather successful in general, in certain limited cases they have been misused to maximise exclusivities and have not always necessarily produced the expected results, including in relation to the investments in orphan and paediatric products in the off-patent sector.

Medicines for Europe supports and recognises the importance of incentives to invest in orphan and paediatric medicines. Any abuses or misuses of the system to maximise exclusivities beyond the intention of the legislation, however, impact effective competition and patient access to treatment. Therefore, while overall the existing incentives seem to be rather successful, there is a need to tackle their misuses and realign pharmaceutical incentives with the clearly defined objectives of the legislation, in line with the priorities described in this paper. In particular:

- **the accumulation of overlapping periods of exclusivity** between an orphan drug and subsequent ones has resulted in delays for the generic version of the first orphan medicine. Concretely, this is related to the interpretation of "similarity" that blocks the approval of generic or biosimilar versions of the first orphan medicinal product despite the expiry of its exclusivity. We trust this was not the intention of the legislation. **This could be tackled by slightly amending the Orphan Drug Regulation to allow generic and biosimilar versions of the first orphan drug to enter the market as soon as its 10-year protection expires, irrespective of further orphan similar products**[1].

[1] See below the actual technical change needed in the legislation in relation to "similarity".

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- **The mechanism to review after 5 years whether the criteria for orphan designation still apply** is foreseen in the legislation and **should be applied in the few cases where the orphan criteria may no longer be in place**.
- **The use of the orphan and paediatric incentives in combination** is often made to maximise the exclusivities while taking advantage of the benefits provided by an orphan status (*i.e.,* development input through protocol assistance, eligibility for MS initiatives, EMA fee reductions). While not all cases can be considered misuses or abuses, it is hard to maintain that certain effects of this use in combination of these incentives were in the intentions of the legislator. **A possible way forward could be to prevent the market authorisation holder of a product that obtained orphan exclusivity from withdrawing the orphan designation in order to obtain an SPC extension afterwards**, as it delays generic/biosimilar medicines competition.

It is of utmost importance to also stimulate competition in the follow-on orphans' field, as well as to stimulate investments in off-patent paediatric products.

Medicines for Europe recommends the introduction of **the following regulatory measures to incentivise competition in the orphan medicines field**:

- Regulatory incentives to support off-patent development
- Tailoring of clinical requirements for follow-on orphan products (particularly for biosimilar medicines)
- Single development for follow-on orphans (one data package) to allow the application in several jurisdictions
- Reduced timelines for pricing and reimbursement decisions
- Pricing and reimbursement tailoring

Medicines for Europe recommends the introduction of **the following measures to stimulate investments in paediatric medicines in the off-patent sector**:

- Single development programme
- Waiving regulatory fees
- Subsidies for R&D
- Pricing and reimbursement tailoring

The position paper below describes in detail these policy proposals.

1. Background

The European Union is conducting a review of the existing pharmaceutical incentives to innovation, following a request by Health Ministers in their Council Conclusions of June 2016, in order to tackle the strong pressure on healthcare budgets caused by the introduction of high-cost innovative products. To this end, the Council Conclusions also underlined the importance of timely availability of generic and biosimilar medicines in order to facilitate patients' access to treatment and improve the sustainability of healthcare systems. The scope of the review would cover the Supplementary Protection Certificate (SPC), the Orphan drug and Paediatric incentives.

To follow up to such request, the European Commission published a Report analysing the use made by pharmaceutical companies of these incentives and their economic impact. In parallel, the Dutch government developed a similar Report. These studies have shown that while the incentives have been widely used and are to be considered rather successful in general, in certain limited cases they have been misused to maximise exclusivities and have not always necessarily produced the expected results, including in relation to the investments in orphan and paediatric products in the off-patent sector.

The European Commission is now focusing on some of the existing incentives, that is the orphan and paediatric regulations (Regulation 141/2000 and Regulation 1901/2006).

2. Orphan Medicinal Products

As highlighted in the above-mentioned studies, since its introduction, the orphan drug regulation has been widely used by pharmaceutical companies, and the trends show that the number of approvals of specialty products designed for smaller populations will increase in the years to come. The 10-year data exclusivity for developing a medicine targeted for a niche population represents a real incentive for pharmaceutical companies and ultimately brings concrete benefits to patients that otherwise would not have access to fundamental treatments.

The main features of the Orphan Drug Regulation 141/2000

The orphan drug regulation provides for an incentive of 10-year exclusivity. In addition, the owner of an orphan product benefits from some free scientific advice as well as fee reductions. During the 10-year period, no generic or biosimilar version of that product or similar product can be approved, making the exclusivity effectively equivalent to data exclusivity. There are two main conditions to obtain an 10-year orphan exclusivity: *i)* the population to address should not be higher than 5 out of 10.000 people, or the disease must be a life threatening/serious chronic condition and the returns expected would not justify the investment; and *ii)* there is no previously authorised satisfactory medicine for that disease. The exclusivity can be extended by two additional years under Article 37 of the Paediatric Regulation if paediatric studies are conducted on the orphan product.

The orphan drug regulation foresees a mechanism for the reduction of the exclusivity period from 10 to 6 years if at the end of the 5th year the product does not meet the orphan criteria anymore. The legislation requires that the 5-year review be triggered by a Member State.

Exceptionally, approval of a subsequent marketing authorisation (MA) for a similar product and for the same therapeutic indication can be granted if *i)* the holder of the first MA gives its consent; or *ii)* the holder of the first MA is unable to provide sufficient quantities of its product; or *iii)* the similar product is safer, more effective or otherwise clinically superior to the first-designated product.

Medicines for Europe Position

Medicines for Europe supports and recognises the importance of incentives to develop orphan medicinal products. Notwithstanding, the association strongly condemns any abuse or misuse of the system aiming at artificially prolonging the exclusivity beyond the intention of the legislator.

Accumulation of exclusivities and interpretation of "similarity" in view of follow-on products

An unintended effect of the orphan regulation, for instance, is the accumulation of overlapping periods of exclusivities. The approval of subsequent products similar to previously approved orphan products has, on occasion, resulted in the accumulation of successive periods of exclusivity with overlapping indications. The effect of this has been to delay market entry of the generic versions of orphan medicines that have already benefitted from 10 years of market exclusivity, resulting in increased costs for patients and healthcare budgets. While allowed by the current version of the Orphan regulation, it seems hard to maintain that this was an intended consequence of the legislation.

In order to tackle this issue, the definition of "similar medicinal products" in Regulation EC 847/2000 (Orphan Regulation Definitions) should explicitly exclude generic and biosimilar versions of orphans that have already benefitted from 10 years of exclusivity from further protection. This would allow, on the one hand, the holder of the orphan product to enjoy all the 10 years of exclusivity and, on the other hand, the generic and biosimilar versions of that product to enter the market at the end of the exclusivity period.

Revision of eligibility after 5 years

The legislation also foresees a review of the conditions for orphan exclusivity after 5 years, to be triggered by a Member State.

Medicines for Europe believes that while the mechanism of review already exists in the legislation, it should be duly used in those, although limited, cases in which the criteria for which the orphan exclusivity was obtained may no longer be fulfilled.

Incentives to develop generic/ biosimilar of orphan medicinal products

When it comes to competition in the follow-on orphans' field, due to the peculiar market dynamics for these particular products, generic and biosimilar companies should be equally incentivised to develop

follow-on orphan products. Currently, there are several market access barriers hindering investments in follow-on orphan medicines, including the limited extension of the market, the difficulty to obtain a comparator product, patient recruitment for clinical trials, *etc*. The traditional development pathway for off-patent medicines is not fit for purpose in relation to follow-on products for small populations.

Therefore, Medicines for Europe calls for the adoption of measures that would stimulate development of follow-on orphans and actual competition on the market at the end of the exclusivity in order to foster access to essential orphan medicines for patients.

i) **Introducing regulatory incentives to support off-patent development:** In the case of originator orphan medicines, incentives (e.g. regulatory, market exclusivities) were put in place to foster new medicine development in therapy areas where unmet needs had been identified and development challenges for smaller populations recognised. The same incentives have unfortunately not been considered yet for follow-on products. Consequently, this situation puts off-patent developers in an unfavourable position. For example, biosimilar developers cannot benefit from the waiving of regulatory or scientific advice fees, nor are they eligible for accelerated market approval for follow-on orphans, despite the societal value they present.

Such incentives or enablers, if in place for biosimilar development, would make the designed pathways more integrated with the life-cycle of innovation and the different speed and approach needed in order to have a regulatory and scientific framework, which is supportive of a multisource medicines environment, once monopolies have expired. When building regulatory pathways for innovation, it is essential to secure early and constructive consideration for follow-on products which contribute to expanding patient access to innovative therapies, most of which have become standards of care, after exclusivities have expired.

ii) **Review the feasibility of clinical requirements for biosimilar medicines of orphan products**: Biosimilar developers are currently required to undertake lengthy and expensive clinical comparability studies, which may bring the total cost of the development up to 150 – 250 million EUR. This makes the development of biosimilar medicines to non-blockbuster medicines extremely complicated. The cost of originator orphan medicine development could be lower or comparable in cost to the development of an equivalent biosimilar medicine (as mainly Phase II studies are performed for originator medicines).

The overall feasibility of performing clinical comparability trials for biosimilars of orphan medicines is even more uncertain when it comes to patient recruitment. The time needed to recruit patients from these limited populations can result in the prolongation of the biosimilar development.

On top of that, access to the comparator products can be very restricted, due to individual treatment programmes or specific access schemes (e.g. dedicated administration centres). Moreover, limited volumes and numbers of batches can be supplied from the market when the product is intended for smaller populations. In order to enable sampling of different reference product batches, a developer would have to wait for a longer period of time than for a larger volume product. Even if the product is available, the acquisition cost of obtaining the comparator product can be very high (example: Eculizumab – estimated to $500.000 per patient per year).

Therefore, clinical requirements for biosimilars should be revisited in consideration of ways to reduce the burden of biosimilar developers such as: waiver or reduced requirements of the clinical comparability studies (especially efficacy and safety) and/or more flexibility allowed in their design, or Member States' support in enhancing the procurement of comparator products.

iii) **Single development for follow-on orphans:** a single development programme for multiple jurisdictions would clearly incentivise companies to develop follow-on products for small population. The investment, economically not viable for only one region, may become more attractive if a population of patients to treat covered several regions. The possibility to source the reference product from one jurisdiction only (with the same stringent regulatory requirements and confirmation that reference products in those regions are comparable), would allow companies to engage in one development programme and avoid a replication of unnecessary and unethical clinical studies to register the same medicine in different regions worldwide *e.g.* USA, Korea, Japan, etc. While reducing costs and wasted resources for both companies and regulatory agencies, this would also speed up the development phase to the benefit of patients.

Streamlining policies in a collaborative manner between different jurisdictions can significantly increase the feasibility of faster, broader and future access for patients around the world. Any adaptation of the generic and biosimilar paradigm will have to be carried out in a coherent way and coordinated between different jurisdictions.

iv) **Reduced timelines for pricing and reimbursement decisions**: once regulatory and IP exclusivities for orphan products expire, generic and biosimilar companies have to go through P&R procedures in the different Member States. In line with the purposes of the Bolar exemption that aims at allowing generic entry as soon as protections expire, the P&R procedures should not further delay market entry of follow-on products. Therefore, P&R systems should reflect this need.

v) **Pricing and reimbursement tailoring**: current pricing and reimbursement rules are not fit-for-purpose and do not deliver sufficient return-on-investment to incentivise off-patent orphan development. This should be reflected in P&R authorities' decisions.

3. Paediatric Medicinal Products

The independent studies abovementioned have shown that while incentives for the development of new paediatric medicinal products are largely used for medicinal products originally developed for adults, the objective of the legislator to develop children-only product has hardly produced any results. Moreover, the existing incentives for the off-patent segment have been used only to a very limited extent, resulting in an ineffective incentive tool.

The features of the Paediatrics Regulation 1901/2006

The Paediatric Regulation provides for the possibility to prolong the Supplementary Protection Certificate (SPC) for 6 additional months. The conditions for obtaining this extension include the application by a company at least 2 years in advance of the SPC expiry and an agreed Paediatric Investigation Plan (PIP). To avoid a double protection, when the owner of an orphan medicinal product conducts paediatric studies, it has to choose whether to keep the orphan exclusivity and obtain a two-year extension to the period of orphan exclusivity or to obtain a 6-month SPC extension. The regulation also foresees a 10-year exclusivity incentive for the development of paediatric medicines in the off-patent sector, the so-called PUMA, obtainable under the conditions that the product is no longer covered by Intellectual Property protection; the product is exclusively developed for use in children; and a Paediatric Investigation Plan (PIP) is agreed.

Medicines for Europe position

Medicines for Europe strongly believes in the importance of incentivising investments in new medicinal products for children. However, while the incentives for investments in paediatric use for patent protected products have been widely used due to the strong benefits enjoyed on the market (*i.e.*, an extension of the SPC protection that, therefore, covers the whole product; in case of PUMA- the exclusivity covers only a paediatric MA), the incentives for paediatric investments in off-patent medicines sector has produced very limited results.

The use in combination of orphan and paediatric incentives

In regard to the use in combination of orphan and paediatric incentives, it is often the case that an owner of an orphan product decides to drop its orphan status in order to obtain an SPC extension rather than obtaining an extension of the orphan exclusivity, since the SPC protection covers the whole product, whereas the orphan exclusivity covers only the paediatric indication.

As a result, in certain cases the use of the two incentives in combination is made to maximise the exclusivity while at the same time the product owner has taken advantage of the benefits provided by an orphan status (*i.e.,* scientific advice and fee reductions). While not all cases can be categorised as misuses or abuses, it is hard to believe that this use in combination of these incentives was in the intentions of the legislator. A possible way forward could be to prevent the owner of a product that

obtained orphan exclusivity from withdrawing the orphan designation in order to obtain an SPC extension.

Incentives to stimulate investments in paediatric medicines in the off-patent sector

As far as the off-patent incentives are concerned, the PUMA has been used only on five occasions. This shows that PUMA alone is insufficient to incentivise the development of off-patent paediatric products, and there is need to enhance the incentive available in the off-patent paediatric sector.

Medicines for Europe believes that new measures should be adopted to stimulate investments:

i) **Single development programme**: this would allow one development process for multiple jurisdictions in the paediatric field.

ii) **Waiving regulatory fees**: as for follow-on orphan products, regulatory fees in the paediatric field are extremely costly and their reduction would be significantly beneficial to encouraging competition in the market.

iii) **Subsidies for R&D**: due to the limited profitability of the paediatric off-patent market, R&D subsidies would incentivise paediatric research in the off-patent sector.

iv) **Pricing and reimbursement tailoring**: current pricing and reimbursement rules are not fit-for-purpose and do not deliver sufficient return-on-investment for paediatric development in case other generic/biosimilar alternatives are available.

4. Conclusions

As described above, the existing incentives for orphan and paediatric products are very important to stimulate investments in these sectors and have been widely used since their introduction. For the generic and biosimilar medicines sectors, any abuse or misuse of the incentives beyond the intentions of the legislation poses a serious risk of delayed market entry. Delayed competition is mainly to the detriment of patients and national health fund budgets. As a consequence, it is of utmost importance that a proper use of the incentives system be ensured and that proper competition is not hampered.

To this end, any attempt to maximise exclusivities beyond the intention of the legislation should be prevented by realigning pharmaceutical incentives with the clearly defined objectives of the legislation, in line with the priorities described above.

Very importantly, the incentives system cannot disregard the potential deriving from investments in the orphan and paediatric sector in the off-patent segment. Therefore, the strong incentives that exist for new orphan and paediatric medicinal products should be mirrored in the off-patent sector, in line with the proposals described in this paper.

Medicines for Europe remains strongly committed to contributing to the improvement of the orphan and paediatric medicines sectors for the benefit of patients.