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EUROPE – Are Revisions of the Orphan Drug Regulation and Adoption of a Regulation on "Unmet Medical Needs" on the Horizon?

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The European Commission (Commission) has released a Staff Working Document concerning its joint evaluation of the Orphan Regulation[1] and the Paediatric Regulation[2] (collectively, the Regulations) (Joint Evaluation)[3] and an executive summary thereof. (Click here for more information.)

The Joint Evaluation assessed the strengths and weaknesses of the Regulations, both separately and in combination with each other; explained past uses of the incentives and rewards; and analyzed the related financial consequences. It is a very important document because it will guide the Commission in proposing changes to the legal framework. The next step should be an impact assessment of the policy options envisaged by the Commission (expected for Q4 2020).

This note gives a brief background of the Joint Evaluation (Section I) and then discusses shortcomings of the Orphan and Paediatric Regulations that were outlined in the Joint Evaluation, first in combination (Section II) and then separately (Sections III and IV). Considering those, we comment and suggest likely changes to the EU legal framework.

Overall, the shortcomings identified by the Joint Evaluation suggests that the Commission could propose:

– the adoption of a new regulation to support the development, availability and perhaps accessibility of medicinal products for unmet medical needs. Given the increasing convergence between the EU and U.S. regulatory systems -- as well as collaboration between the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) -- the new EU rules could be influenced by U.S. programs such as priority review vouchers in reward for certain types of investment.

– a revision of the Orphan Regulation; and

– amendments to the Paediatric Regulation, albeit probably through the revision of other regulations (Orphan Regulation and Regulation on

Supplementary Protection Certificates) or the adoption of new regulation on unmet medical rather than a revision of the Paediatric Regulation itself.

The revision of the legislative framework will take a few years. In the meantime, regulators will most probably not stay inactive and will try addressing the shortcomings that can be fixed by guidelines or practice.

Companies involved in the development of orphan and pediatric medicinal products, as well as in antibiotics, should closely follow the future of the discussions around the revision of the legislative framework and, whenever needed, get involved in those discussions. More importantly, they should anticipate evolution of the EU legal framework, especially for orphan drugs and (high) unmet medical needs, and its impacts on today's development and investment.

SECTION I: JOINT EVALUATION – THE BASICS

The Joint Evaluation was based on previous independent studies ordered by the Commission[4], previous reports from the Commission and the EMA[5], and information from stakeholders.

On the basis of that wealth of data, the Commission assessed five aspects of the Regulations (operating in combination and separately) – effectiveness, efficiency, relevance, coherence, and EU added value – that the executive summary classifies in three categories: development and availability, incentives, and accessibility.

The main conclusions of the Joint Evaluation are that, while the Regulations have played their intended role:

- they did not sufficiently support, and are not suited to encourage investment in, the development of medicinal products in areas with unmet medical needs and no or very low profitability; and
- they did not ensure patient accessibility to authorized orphan and pediatric medicinal products. Accessibility refers to both the actual marketing of a product (availability on the market) and market access (pricing and reimbursement).

With regard to the Orphan Regulation, the main conclusion is that orphan exclusivity (called "market exclusivity" in the EU) should no longer be a one size-fits-all incentive, but rather should be tailored to the anticipated profitability, level of investment, or type of application that may be required for marketing authorization (MAA).

Ill-tailored rewards are also the main point of criticism for the Paediatric Regulation.

SECTION II: JOINT EVALUATION OF THE COMBINED REGULATIONS

1. Conclusions of the Joint Evaluation

Development and Availability — The Joint Evaluation found that the Regulations have fostered the development and availability of medicinal products for rare diseases and for pediatric patients. However, neither the Orphan Regulation nor the Paediatric Regulation has adequately supported development in areas where the need for medicinal products is the greatest. In practice, medicinal products have been developed in more profitable therapeutic areas, and the number of products targeting those areas is increasing. Given that the Regulations have no tools to boost development in specific therapeutic areas, however, scientific leads, market forces and revenue expectations continue to influence investment decisions – leaving various therapeutic areas unaddressed.

This outcome calls into question the appropriateness:

- in the rare diseases area, of the prevalence criteria (fewer than 5 in 10,000 patients) for identifying rare diseases which warrant specific support; and
- in the pediatric area, of the extension of the term of the supplementary protection certificate (SPC extension) as the main pediatric reward (an SPC extension brings greater benefits for products with larger sales volumes, and most such medicinal products are developed for use in both adults and children, rather than exclusively for children).

Accessibility. **--** The medicinal products supported by the Regulations are not accessible by patients equally in all EU countries. This is mainly due to factors outside the scope of the Regulations such as strategic launch decisions by pharmaceutical companies and national pricing policies and reimbursement systems. Favorable market conditions (impacted by reimbursement and pricing, corporate taxation, and coverage of healthcare costs) significantly affect availability on the market.

The Joint Evaluation underlines that, hopefully, the future EU legislation on health technology assessment (HTA) will provide more convergence and coherence among national regimes and thereby support accessibility.

King & Spalding (K&S) Comment: Certain EU Member States have complained about the lack of medicinal products on their markets, and discussions about the actual marketing patterns of centrally authorized medicinal products (relevant to orphan drugs and many pediatric medicinal products) are ongoing. The issue has already been partly resolved since the Commission now subjects the authorization of friendly generics and biosimilars of centrally authorized medicinal products to an actual marketing wider than that of the innovative products. However, the Pharmaceutical Strategy foresees that, as part of the review of the pharmaceutical legislation, the incentives would be linked to obligations and "market launch" is expressly mentioned.

Inefficiencies. – Both Regulations use concepts that could be challenged by scientific developments. Currently, legal provisions are directly linked to the concept of disease or condition. The Joint Evaluation concluded that these should be amended to ensure that the Regulations accommodate new scientific developments.

K&S Comment: This is a key issue. On the one hand, orphan designations are granted for a specific condition, and the significant benefit of the future drug must be demonstrated over treatments for the same condition. On the other hand, the adult condition remains the key reference for most pediatric investigation plans (PIP). The term "condition" is already defined in several guidelines. Until a few years ago, the EMA relied on the WHO's 10th International Classification of Diseases (ICD-10) as reference for applying both Regulations. It now also relies on the MedDRA even though this classification is based on safety rather than clinical observations and thus is not appropriate for deciding on clinical development.

As more and more diseases/conditions are identified due to scientific and technological progress, the new definitions will have to be flexible enough for the future regulation not to be obsolete in a few years. Moreover, the same definitions and references (ICD-10 vs MedDRA) should obviously be used consistently across regulations. Currently, the two relevant EMA committees work together to ensure that the condition for the orphan designation is the same as this for the PIP, but a formalization of this practice would be useful.

2. Possible Change to the EU Legal Framework - Adoption of a New Regulation on Unmet Medical Needs?

The key question raised by the conclusions above is not whether the EU legal framework will be revised but whether the revision should replace the Regulations with a new regulation on unmet medical needs, or amend the Regulations to correct inefficiencies and enable them to address unmet medical needs and accessibility. The answer is both.

A New Regulation on Unmet Medical Needs. – Several statements in the Joint Evaluation suggest the adoption of a specific legal regime to address (high) unmet medical needs. The Joint Evaluation mentions that rare diseases can no longer be viewed as a homogeneous group for which no treatments are available, and that more differentiated tools may be needed to direct investments to the specific areas. The same applies to the pediatric area, as not enough "purely" pediatric products are developed, and to antibiotics, which are grouped with orphan and pediatric medicinal products (due to the lack of return on investment).

The Commission thus could propose a new regulation on (high) unmet medical needs that would cover certain orphan and pediatric medicinal products as well as antibiotics. This would be in line with the Pharmaceutical Strategy. This also would be a challenging exercise.

The very first challenge would be the legal definition of "unmet medical need". A definition already exists, but in the narrow setting of conditional marketing authorizations. The concept should be flexible enough to cover scientific and societal evolution.

Another challenge would be to find the appropriate incentive. The current pharmaceutical incentives are all based on protection against competition, and such incentive may not be well-tailored to unmet medical needs, as competition is much less likely to occur (at least fair competition from other authorized medicinal products). Other types of incentives must be relied upon such as regulatory incentives or even reimbursement incentives. The "right" incentive for antibiotics is an old debate, which will now have to be resolved.

Regulatory incentives could be regulatory vouchers or PRIME designations. A 'Priority Medicines' (PRIME) designation is among the best – if not the best – supports for development, availability and accessibility of medicinal products. The closest equivalent in the U.S. system is the Fast Track Designation, which provides for expedited review and interactive development support. Currently, the EMA only grants PRIME designations to a few products for unmet medical needs. Until the EMA has the resources to use this tool more extensively, PRIME could be automatically granted to all medicinal products for unmet medical needs.

A reimbursement incentive would be equally or even more attractive as market access is the key obstacle for many medicinal products. Such incentive would also protect medicinal products for unmet medical needs against unfair competition from hospital preparations. The future regulation could at minimum require the Member States to recognize an "unmet medical need" status decided at the EU level, and to adopt national measures to ensure and accelerate accessibility to their market. Pilot programs for reimbursement of antibiotics started in a few countries, which could be extended to all medicinal products for unmet needs as incentives.

But no provision on pricing and reimbursement. The Joint Evaluation insists that the Regulations do not include a provision to influence accessibility to authorized medicinal products, but a new regulation on unmet medical needs is unlikely to address fully the issue of accessibility. The new EU regulation could impose an obligation to place and maintain the medicinal products on each national market and even force national authorities to recognize unmet medical needs, but it cannot impose specific rules on pricing and reimbursement as those remain (almost) purely national matters. Yet, they are keys to accessibility – it is not a coincidence that more orphan and pediatric medicinal products are marketed in the EU countries with the most favorable market access conditions. Hopefully, the national governments will support medicinal products for unmet medicinal needs through reasonable pricing and reimbursement programs.

Redirecting EU Funding. - In parallel, the Commission could redirect most EU public funding to therapeutic areas with unmet medical needs, provided, however, that, for each specific research project, the funding and its continuation are subject to an actual impact on public health other than a scientific publication. A special fund could be created for research in treatment for unmet medical needs.

The U.S. as a Model? - Insofar as the EU and the U.S. already collaborate in areas exhibiting high unmet medical needs (orphans, pediatrics and antibiotics), the EU could use U.S. orphan drug and pediatric ideas as a model for future regulation. As one example, the U.S. has used a "voucher" program to create incentives for sponsors to develop new active ingredients to treat rare pediatric diseases. If detailed qualifying criteria are satisfied, at the time of pediatric product approval the sponsor will receive a "voucher" – which it can use itself or sell to another developer. The voucher then expedites FDA's review of any other product (not necessarily for unmet medical need) and potentially gets that product to market faster.[6] As a second example, a unique, 5-year add-on period of market exclusivity was created, including "fast track" designation yielding enhanced regulatory interactions, and priority review of submitted applications, to encourage the develop of new antibacterial and antifungal drugs for human use to treat serious or life-threatening conditions.[7] Other possible mechanisms such as funding through government-partnered research (e.g., sponsored by government biodefense agencies) or making payments to sponsors at the time of actual market-entry have been attempted or explored, as part of the efforts to spur investment in this area of limited inherent market incentives.

If the EU decides modelling the U.S., a key point is to ensure convergence and thereby support global development. Divergent requirements to obtain incentives are more cumbersome than divergent or even no incentives. Convergence is critical for the pharmaceutical industry, in particular companies developing medicinal products for small populations, many of which are European small-medium companies (SMEs).

What About Antibiotics? - A new regulation on unmet medicinal needs would incentivize the development and marketing of antibiotics but would most probably not address the other issues associated to this very specific category of medicinal products. Like for orphan and pediatric medicinal products, a specific regulation on antibiotics should be adopted or specific rules on antibiotics should be added to the pharmaceutical legislation for human use as they were last year to the pharmaceutical veterinary legislation.

SECTION III: JOINT EVALUATION OF THE ORPHAN REGULATION

The Joint Evaluation highlighted substantial shortcomings and thereby strongly suggested that the Orphan Regulation will be revised. Some shortcomings, however, could be addressed by amending guidelines rather than the legislation and thus could be resolved more quickly.

When explaining the shortcomings of the Orphan Regulation, we will suggest possible changes to the EU orphan framework and/or provide comments.

1. Development and Availability

The Joint Evaluation stressed the following shortcoming when examining the Orphan Regulation operating in combination with the Paediatric Regulation:

Shortcoming	***What could happen?***
The appropriateness of the prevalence criteria (fewer than 5 in 10,000 patients) for identifying rare diseases which warrant specific support	The threshold of prevalence criterion could be lowered; or a new element could be included into the prevalence criterion; the prevalence criterion could be replaced by another.

K&S Comment: This change would be detrimental to the development of orphan drugs. It would seek to and result in reducing the number of orphan designations; however, it is the granting of orphan designations that triggers private investment in SME and contributes to the development of orphan drugs. In any event, such change would no longer necessary if specific rules on unmet medical needs are adopted.

Note: The Joint Evaluation "defines" an ultra-rare disease as a disease affecting less than 1 patient in 10,000 (the same "definition" is included in the Clinical Trials Regulation). Yet, it does not suggest adopting a new, specific definition or rules for ultra-rare diseases. This probably results from the fact that it focuses on unmet medical needs, regardless of the prevalence of the disease/condition.

Shortcoming	***What could happen?***
Legal definitions	New legal definitions, in line with the legal definitions to be adopted for the new regulation on (high) unmet medical needs, will be added to the Orphan Regulation

The Joint Evaluation indicates the following shortcomings when examining the Orphan Regulation alone:

Shortcoming	***What could happen?***
The successful development from orphan designations to actual, authorized orphan medicinal products remains	Probably nothing relevant to success rate, as the Commission seeks to limit the number of medicinal

slow in comparison to the U.S. and Japan, which can be explained by different eligibility criteria.	products for a given rare disease and thereby redirect investment into other rare diseases.

K&S Comment: Remarkably, the Joint Evaluation did not question the criterion of having to show "significant benefit" compared to existing treatments, or the two-step process for obtaining orphan status -- although both of these prevent orphan designations and deter the development of new orphan drugs (not only in therapeutic areas where medicinal products are already authorized but also in other therapeutic areas). They are probably not seen as issues since the criterion of significant benefit presupposes that medicinal products are already available for the rare disease concerned. However, the problem is more complex and includes the concepts such as the interpretation of "satisfactory method of treatment", and the specific evidence required for companies to demonstrate significant benefit. For example, the Commission added compounded "preparations" to the list of potential satisfactory methods of treatment; this de facto requires companies to demonstrate that their medicinal products bring a significant benefit over unproven, and generally unregulated pharmacy preparations. Such evidence being very difficult, if not impossible, to bring (as is recognized by the Joint Evaluation), rare disease patients end up being treated with individually compounded preparations rather than fully tested, assessed, and approved medicinal products.

Shortcoming	***What could happen?***
The orphan-qualifying criterion of "insufficient return on investment" has failed to attract companies, although the Orphan Regulation would have supported the development of products for which companies cannot expect sufficient return on investment such as antibiotics.	Through amendments of guidelines: Evidence for the criterion "insufficient return on investment" could be simplified or delayed so that companies can actually use it.

Shortcoming	***What could happen?***
Advances in science (such as personalized medicine and biomarkers) should not be allowed to result in unnecessary multiplication of rare diseases from common diseases (sub-setting) and related proliferation of orphan exclusivity periods.	Orphan exclusivity period could be shorter in cases of sub-setting. Through amendments of guidelines: Conditions for sub-setting of diseases could be made more stringent

K&S Comment: The risk seems remote given that the EMA has a longstanding and restrictive practice with regard to sub-setting. Sub-setting is only allowed if the applicant demonstrates that it is scientifically justified to treat the subset differently because the future product only has effects in this specific subject. Sub-setting, therefore, is delimited by the condition and does not depend on the nature of the product.

2. Incentives

The EU incentives for orphan drugs are market exclusivity, protocol assistance and fee waiver/reduction. EU countries also provide incentives such as tax exemption, accelerated reimbursement processes, etc.

The Joint Evaluation concluded that, despite theoretically increased costs for healthcare systems, incentives remain important to encourage the development of orphan drugs because patients with rare diseases benefit from improved quality of life. However, several issues related to the incentives and, in particular, orphan exclusivity, were noted.

Orphan Exclusivity. - There is no evidence to doubt the effectiveness of the orphan exclusivity concept,[8] but the orphan exclusivity period should depend on the level of rarity of the disease and the scale of investment in order to avoid overcompensation.

Shortcomings	***K&S Comments***	***What could happen?***
Orphan exclusivity may have led to overcompensation for orphan drugs with an annual turnover above 100	*While this change is justified in some situations, tailoring will be difficult to design.*	Orphan exclusivity could be refined so that its duration depends on expected profitability.

million Euros (14% of orphan products). This calls into question the length of the orphan exclusivity (10 years).	*Furthermore, tying the orphan exclusivity to evidence of profitability or level of investment in R&D could make it ineffective and thus deter companies for investing in rare diseases.*	
The Orphan Regulation allows for a shortening of the orphan exclusivity period once a medicinal product becomes commercially successful, but the EU Member States have never triggered the procedure because it is too difficult to provide the necessary evidence.	*The reduction of the orphan exclusivity period is set forth by law but has been implemented by a Commission guideline[9] that sets the conditions for applying the reduction. That guideline was only adopted in 2008, after intense discussions among the EU countries. It therefore is interesting that the EU countries complain about too stringent conditions for reducing the exclusivity period.*	Through amendments of the relevant guideline: Conditions for a reduction of the orphan exclusivity period will be amended so that the mechanism can be used more easily.
This finding goes hand-in-hand with the fact that only one application for orphan designation has been received under the criterion "insufficient return on investment." This shows that it is hard to estimate future investments and returns before the therapeutic indications have been established and the appropriate selling price is clear.	*This finding alone should convince the regulators and legislature that legal provisions based on development costs or return on investment will remain unused, unless perhaps if they apply for new uses of a marketed medicinal product.*	
Low revenues do not necessarily mean "insufficient" returns on investment, depending on the specific situation, the development costs, and potential generics. However, it is difficult to determine an appropriate range of rewards (e.g., higher for a reduced return on investment, or lower when no reward is needed) without precise data on development costs and complex market analyses.		
Literature suggests a slower price fall upon generic entry for an orphan drugs; however, generic competition has only been observed for very few products to date because only a few orphan exclusivities have expired. This may also result from the fact that an application for a generic can be submitted only after expiration of the orphan exclusivity period.	*The EMA actively supports the development of generic (orphan) drugs by adopting scientific guidelines on bioequivalence and other requirements for the active substances concerned. Yet, the generic (orphan) market remains small. The fact is that the markets for orphan drugs are in essence small and thus unattractive for generics.*	Generic competition could be supported by allowing generic MAA before expiration of the orphan exclusivity period.

Protocol assistance. - Developers of orphan drugs, particularly small-medium companies (SMEs), have benefited from free scientific advice that seems to have improved the possible success rate of development.

Shortcoming	***What could happen?***

SMEs may not necessarily bring orphan drugs to the market themselves as promising medical products are often acquired by larger pharmaceutical companies at a late stage of development.	Fee waiver/ reduction might have to be (wholly or partially) 'reimbursed' to the EMA when an SME sells its orphan drug to a non-SME.

Fee waiver/reduction.

Shortcoming	***What could happen?***
Research institutes and academia cannot benefit from the incentive because it is reserved to SMEs.	All incentives will be extended to academia.

3. Accessibility

Shortcoming	***What could happen?***
The Orphan Regulation does not impose an obligation to market an authorized orphan drug in all EU countries.	An obligation to place orphan drugs in every national market within a certain period after the granting of the MA, could be added.

K&S Comment: The legal provisions could be modelled on Article 33 and 35 of the Paediatric Regulation. See also comments below on the Paediatric Regulation.

Shortcoming	***What could happen?***
The Orphan Regulation does not contain any provisions on transparency of R&D costs or of return on investment to facilitate downstream decisions that would influence the affordability and accessibility of orphan drugs.	

K&S Comment: The Orphan Regulation should not require the submission of information on R&D costs or return on investment to facilitate pricing and reimbursement decisions. Not only are companies most probably unable to provide such information (as the Joint Evaluation recognizes), but also transparency of development costs for pricing and reimbursement purposes should be discussed more generally and in the context of HTA. The potential effect of such transparency on the EU market warrants comprehensive and focused impact assessment and discussions.

4. Inefficiencies

Shortcoming	***What could happen?***
'Indication stacking': Almost 17% of orphan drugs are authorized for two or more orphan indications, each referring to distinct orphan conditions and, as such, being entitled to multiple periods of orphan exclusivity. However, the additional orphan exclusivity period needed to recover the additional costs of R&D is often unclear. Moreover, additional orphan indications have been identified as a barrier to developing generic orphan medicinal products.	Orphan exclusivity could be refined so that its duration depends on the level of investment in R&D. The Joint Evaluation suggests that an option could be to reduce the 10-year period for each new indication or to calculate prevalence for all indications (cumulative prevalence) rather than for each indication.

Shortcoming	***What could happen?***
Some medicinal products are well-established (such as a compendial formulas) before being repurposed for orphan diseases (19%). Producers may substantially increase the price of a drug that was previously available at a lower	Orphan exclusivity could be refined so that its duration depends on expected profitability, type of MAA or level of investment in R&D.

price, without clear relation to actual R&D costs of the new product. Although price setting lies beyond the remit of the Orphan Regulation, additional orphan exclusivity seems to be a triggering factor. Therefore, the Joint Evaluation recommended that consideration be given to differentiated incentives, depending on the type of MAA or the level of investment in R&D.	

K&S Comment: One cannot immediately discount the need for incentives to develop a known product for a new use. Repurposing old active substances for rare diseases generally requires substantial studies and significant pharmaceutical investment. The Commission previously created the STAMP Working Group, whose mission includes repurposing, and in March 2019, that working group published a "proposal for a framework to support not-for-profit organizations' in drug repurposing". Repurposing benefits rare disease patients and, as such, deserves support whether it comes from industry or academia. The same does not always apply to preparations (i.e., compounded products).

Shortcomings	***What could happen?***
There may be room for simplification and streamlining of internal processes including different EMA scientific committees to avoid the risk of inconsistencies and delays.	Through amendments of guidelines: Internal processes that include different EMA scientific committees will be simplified and streamlined to ensure alignment and coherence of procedures.
Furthermore, some procedures create additional administrative burdens, which may no longer be necessary and proportionate (e.g. the obligation for sponsors to submit an annual report on the orphan designation to the EMA).	Unnecessary administrative procedures could be removed from the Orphan Regulation. Through amendments of guidelines: Administrative documents and processes will be simplified or reduced.

Shortcoming	***What could happen?***
Many EU and national initiatives and programs are aimed at boosting the development of treatments for rare diseases. However, no direct link can be made between publicly funded research projects on rare diseases and the orphan drugs actually developed because both the Orphan Regulation and specific research programs lack monitoring arrangements.	Monitoring arrangements could be added in the Orphan Regulation and/or specific research programs

Publicly funded research is an important tool to support development in high unmet needs, but the Joint Evaluation concluded that there is insufficient information to show whether public funding of research programs has produced new orphan or pediatric medicinal products for unmet medical needs.

SECTION IV: JOINT EVALUATION OF THE PAEDIATRIC REGULATION

The Joint Evaluation suggests that Paediatric Regulation will not be revised but effectively amended through revisions of other regulations, i.e. in a very focused manner.

When explaining the shortcomings, we will suggest likely changes to the EU pediatric framework and/or provide comments.

1. Development and Availability

The Joint Evaluation stressed the following shortcoming when examining the Paediatric Regulation in combination with the Orphan Regulation:

Shortcoming	***What could happen?***
This calls into question the appropriateness of the SPC extension as the main pediatric reward	Most probably nothing because replacing the SPC extension as the main reward would be a key change to the Paediatric Regulation

Shortcoming	***What could happen?***
Legal definitions	Legal definitions could be added to the Paediatric Regulation through the adoption of a regulation specific to (high) unmet medical needs and the revision of the Orphan Regulation

The Joint Evaluation indicates the following shortcomings when examining the Paediatric Regulation alone:

Shortcoming	***What could happen?***
The Joint Evaluation only mentions that the current design of the pediatric requirement may not capture all adult developments that could potentially benefit children. It gives the following example: medicinal products are increasingly studied based on their mechanism of action, and the mechanism of action of a product developed to treat an 'adult-only' disease could also be helpful in treating a different disease in children. However, the Paediatric Regulation exempts products for adult-only diseases from the obligation of designing a PIP.	No change is needed – see K&S comment below.

K&S Comment: The Paediatric Regulation is not clear about the reference to the PIP for new medicinal products, but, in practice, the EMA does rely on the mechanism of the action to determine the scope of the PIP and grant waivers - see EMA Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver), 30 July 2012.

The PIP and PIP procedure have been constantly and heavily criticized by companies. Nonetheless, the Joint Evaluation is basically silent on the rules relating to the PIP and PIP procedure except for two inefficiencies that should be remedied (see below). This silence probably results from the fact that the issues arose from the interpretation and application of the Paediatric Regulation by regulators and, as such, are being addressed through updates of guidelines and the EMA-Commission Joint Action Plan[10], which explores possible ways to improve the PIP procedure.

Despite the industry's criticism, only little improvement has been seen so far. And it is unclear if and how the Joint Action Plan will be implemented. So far, the Commission and the EMA have not disclosed information on the implementation. Yet, the Joint Action Plan is supposed to involve all stakeholders and to end in December 2020. Hopefully, a revised version of the Commission guideline on PIP will soon be released by the Commission for public consultation.

2. <u>Incentives</u>

The Joint Evaluation concludes that incentives remain relevant to encourage the development of pediatric medicinal products. They have increased costs for healthcare systems, but the increase is justified because the benefits for children appear to outweigh the costs imposed on industry and society. However, fundamental issues undermine the pediatric reward system.

SPC Extension

Shortcoming	***What could happen?***

Obtaining an SPC extension may be difficult and complex as companies have to request it individually at the various national patent offices. Furthermore, the SPC extension resulted in over-compensation in some cases and under-compensation in others.	The Joint Evaluation specifies that the rules on the SPC extension could be improved through revision of the SPC Regulation

Orphan Extension

Shortcoming	***What could happen?***
This reward has rarely been used and has thus done little to boost development in areas of unmet pediatric needs. Developers consider it less valuable than the SPC extension.	The orphan reward could be improved through revision of the Orphan Regulation.

PUMA

Shortcoming	***What could happen?***
The same goes for the PUMA (pediatric use MA) scheme, designed to channel EU research funds into development of new pediatric indications in off-patent medicinal products. Factors beyond the Paediatric Regulation are the main reasons for the failure of the PUMA scheme (difficulty of obtaining higher prices and reimbursement; difficulty in conducting pediatric clinical trials of old medicinal products that are already available on the market and often widely used off-label).	Nothing. The Joint Evaluation states that the PUMA will be kept as such.

K&S Comment: The Joint Evaluation ignores that the Paediatric Regulation expressly provides for the creation of a public fund specifically dedicated to the pediatric development of old active substances (MICE). The MICE was never created. Rather, some random public financing occurred through FP7 and FP8. The creation of MICE could boost PUMA.

In general

Shortcoming	***What could happen?***
The use of rewards was limited to 55% of the potentially eligible PIPs completed, which indicates that the current system has certain limitations.	Most probably nothing. Adding or expanding a reward to cover new medicinal products without patent protection, such as vaccines, would be very useful. This, however, is probably not a priority for the Commission that does not want to increase pharmaceutical incentives.

K&S Comment: Offering a pediatric reward for new medicinal products without SPC and orphan status would support the development of exclusivity pediatric products. The choice of the right reward is not easy. For example, the EU could model after Switzerland and create a "pediatric SPC".

3. Accessibility

Shortcoming	***What could happen?***
While the Paediatric Regulation does include some instruments to ensure that a pediatric product is actually launched in all EU countries, accessibility of pediatric products on EU markets can still be problematic since the pediatric launch is closely linked to the launch of the adult equivalent	

K&S Comment: The Paediatric Regulation does not expressly mandate the actual marketing of pediatric products in each national market but ties the obligation to the prior marketing of the product, e.g., to the adult population. The issue highlighted by The Joint Evaluation thus is limited to formulations that have been developed especially for children, at the Paediatric Committee (PDCO) request. For cost and logistics reasons, those formulations typically are formally launched

in a few countries but are available upon request in all EU countries, which overall allow children to get access to the pediatric products.

4. Inefficiencies

Shortcoming	***What could happen?***
The SPC extension is awarded even if the outcome of the PIP is negative, i.e. does not lead to a new pediatric indication.	No change is needed. Any pediatric research contributes to reducing off-label use in children.

K&S Comment: The SPC extension is intended to drive pediatric research and generate data about the use of a medicinal product in young patients. Both positive and negative results are valuable to prescribers and parents, and the completion of a pediatric assessment should be rewarded (regardless of the nature of the results). This premise, which was the starting point of the Paediatric Regulation back in 2006, should not be questioned.

Shortcoming	***What could happen?***
Lack of coordination among regulatory authorities worldwide, although this has been largely resolved by the creation of a "pediatric cluster" (EMA, FDA, Health Canada, JPMA).	

K&S Comment: While the Pediatric cluster is active, its actual impact is difficult to assess due to a lack of transparency of communications among regulators. Yet, global development is key for gene therapy products, personalized medicinal products, orphan drugs, and all other medicinal products with a small target population. More transparency would be welcome, for various reasons.

Shortcoming	***What could happen?***
Delay in completion of the PIP due to competition among companies to conduct trials in small population.	Ongoing changes through the EMA-Commission Joint Action Plan

K&S comment: This inefficiency could be resolved if the same pediatric trials for different active substances were better scheduled or even not required where several medicinal products are already available for the condition/disease, be it with other active substances.

Shortcoming	***What could happen?***
Administrative burden, especially related to the PIP modifications.	Ongoing changes through the EMA-Commission Joint Action Plan

Shortcoming	***What could happen?***
The pediatric legislation itself is perceived as burdensome by industry because it requires companies to establish the PIP -- including the design of the pediatric trials – with the EMA at an early stage of development. At those early stages, however, overall product development may be subject to considerable change, requiring changes to the PIP, and companies thus must submit requests for modifications to the EMA. This is particularly problematic in the case of an innovative trial design, where development plans are often shaped by the results obtained in previous phases of clinical development. National authorization of pediatric trials is potentially burdensome since it may, in	Ongoing changes through the EMA-Commission Joint Action Plan

certain cases, contradict what has already been agreed on in a PIP.	

The Joint Evaluation stresses that these aspects should improve with the application of the new Clinical Trials Regulation (better harmonization of the conduct of multinational trials) and the implementation of the EMA-Commission Joint Action Plan.

SECTION V: CONCLUSION

The Joint Evaluation insists that when designing the options for updating the legal framework, the Commission will have to take into account that (i) the Regulations are only one element in a set of measures designed to improve the situation of patients (timely diagnosis; availability of expert centers in the EU; public interventions); and (ii) a balance is needed between the needs of fostering innovation and ensuring the availability of and access to medicines for patients. These aspects are closely linked to the key objectives of the Pharmaceutical Strategy for Europe.

The Joint Evaluation leaves no doubt as to the need for a revision of the Orphan Regulation and, possibly, the adoption of a regulation specific to (high) unmet medical needs, with small amendments to the Paediatric Regulation. The processes will take several years. In the meantime, the Commission, the EMA and perhaps the Member States will adopt and amend guidelines to correct some of the shortcomings identified in the Joint Evaluation.

Companies involved in the development of orphan and pediatric medicinal products, as well as in antibiotics, should closely follow the discussions around revision of the legislative framework and, whenever needed, get involved in those discussions. They should also anticipate evolution of the EU legal framework, especially for orphan drugs and (high) unmet medical needs, and its impacts on today's development and investment.

[1] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.
[2] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/200.
[3] European Commission, 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, 11 August 2020.
[4] European Commission, Study to support the evaluation of the EU Orphan Regulation, July 2019; European Commission, Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe, May 2018; Technopolis and Ecorys, Study on the economic impact of the Paediatric Regulation, including its rewards and incentives, Dec. 2016.
[5] European Commission, State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation, Report from the Commission to the European Parliament and the Council, 2017. EMA, General report on the experience acquired as a result of the application of the Paediatric Regulation, 10-year Report from EMA to the European Commission, 2017.
[6] 21 U.S.C. § 360(ff). When it established this provision, the U.S. Congress included a “sunset” (expiration) provision. If the program is deemed successful, it must be renewed and can be modified.
[7] 21 U.S.C. § 355f.
[8] The real effect of market exclusivity was calculated to be an additional protection period averaging 3.4 years (in addition to patent/SPC protection), and the corresponding value of this reward was estimated at 30% of revenues from sales of orphan medicinal products.
[9] European Commission, Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products, 23 Sept. 2008.
[10] EMA and European Commission, Action plan on paediatrics, Oct. 2018.