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How EU's New Pharma Incentives May Affect US Cos.

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The European health landscape is being shaken, and the outcome will have significant impacts for U.S. pharmaceutical developers and manufacturers that market products in Europe.

In November 2020, the European Commission adopted a pharmaceutical strategy[1] with several directive axes, including innovation for medicinal products directed at unmet medical need; accessibility, including security of supply and shortages; and affordability through a competitive market.

The pharmaceutical strategy officially started several legislative amendments and revisions, in combination with several initiatives, including the creation of the Health Emergency Preparedness and Response Authority[2] — a new authority equivalent to the U.S. Biomedical Advanced Research and Development Authority — and of the European Health Data Space,[3] both heritages from lessons of the COVID-19 pandemic.

In parallel, the Medical Devices Regulation and the In Vitro Diagnostics Regulation, as well as the Clinical Trials Regulation, became applicable while the revision of the Blood, Tissues and Cells Legislation progressed, leading to a legislative proposal for a regulation on substances of human origin.[4]

Focus on environment in the pharmaceutical sector also increased. Only the regulation on advanced therapy medicinal products[5] remains untouched so far, despite criticism.

Two legislative revisions concern the heart of the European pharmaceutical regulatory system: the revision of the General Pharmaceutical Legislation and the revision of the Orphan and Paediatric Legislation. This article analyzes the European Commission's current policy proposals for reaching the objectives of the revisions, with an emphasis on pharmaceutical incentives.

General Background for the Revisions

Following the publication of the pharmaceutical strategy, the European Commission's Directorate General for Health and Food Safety released road maps — which generally explain the reasons and

objectives for the revisions[6] — and launched several consultations. It also linked the two revisions as the legislations concerned set out pharmaceutical incentives, e.g., regulatory protections.

Legislative proposals were expected by the end of 2022, but in August, the European Commission's Regulatory Scrutiny Board rejected the impact assessments the directorate general submitted. As a result, the directorate general is again working on the impacts assessments, and the release of legislative proposals has been pushed back to June 2023.

Assuming that this deadline is met, the revisions will most probably be voted on in 2025, or even 2026, as new European elections will take place in 2024.

Rejection by the Regulatory Scrutiny Board means that the directorate general must better justify the policy proposals made in the impact assessments, in particular its preferred options. The directorate general is not required to change these proposals, and many believe that it will not do so.

The impact assessments are the first pieces of information on the directorate general's general direction for the revisions. They outline the policy proposals that have been envisaged and assessed by the European Commission to reach the different objectives for the revisions.

Revision of the General Pharmaceutical Legislation

Directive 2001/83[7] sets out the basic rules for all medicinal products and the decentralized marketing authorization procedure, and Regulation 726/2004[8] sets out the centralized marketing authorization procedure, the rules applicable to centrally approved medicinal products, and the European Medicines Agency — collectively General Pharmaceutical Legislation.

They are the cornerstones of the EU pharmaceutical legislation and regulatory system for placing medicinal products on the EU market.

The article does not explain in detail the scope and the reasons for the revision of the General Pharmaceutical Legislation. We refer to the pharmaceutical strategy and the relevant road map.

First, the European Commission wants greater harmonization, which would require a single regulation to replace both Directive 2001/83 and Regulation 726/2004, as it was the case for veterinary products in 2019.

Secondly, to integrate the pharmaceutical strategy, the European Commission set five objectives to the revision:

1. To promote innovation, in particular for unmet medical needs;
2. To create a balanced system that supports affordability but rewards innovation;
3. To ensure access for patients, with special attention to enhancing security of supply chains;
4. To reduce the environmental footprint; and
5. To reduce regulatory burdens and provide a flexible regulatory framework.

Three Policy Options

The directorate general proposed three policy options to reach the first four objectives, each of which covers the same topics: pharmaceutical incentives, antimicrobial resistance,[9] environment and

security of the supply chain. The options are accompanied by the same common measures designed to reach the fifth objective.

Option A

Pharmaceutical incentives	Same regulatory protection as now: eight-year data exclusivity + two or three-year marketing protection[10] for medicinal products that contain a new active substance.[11] + One-year data exclusivity, provided that the product meets an unmet medical need, or UMN. + Six-month data exclusivity for comparative clinical trials. + Six-month data exclusivity, provided that the product is launched in all national markets within five years of marketing authorization.
Antimicrobial resistance	Transferable data exclusivity voucher + one-year data exclusivity.
Environment	Same environmental risk assessment requirements as now.[12] Additional information on environmental sustainability of supply chain actors to be provided in marketing authorization applications.
Security of supply chain	Same requirement for notification of withdrawals as now: Two months.

Option B

Pharmaceutical incentives	Six-year data exclusivity + two-year marketing protection. + Two-year data exclusivity, provided that the product (1) meets an UMN or there is no return on investment, to be proved by means of research and development costs, and (2) is launched in the majority of the national markets.
Antimicrobial resistance	Development and marketing authorization or financing of a fund for the development of novel antimicrobials. Measures to ensure prudent use of antibiotics.
Environment	Increased environmental risk assessment requirements by adding assessment of manufacturing.
Security of supply chain	Same requirement for notification of withdrawals as now: Two months.
	Public disclosure of state funding received.

Option C

Pharmaceutical incentives	Same regulatory protection as now (eight-year data exclusivity + two or three-year marketing protection), provided that the product is launched in all national markets within two years of marketing authorization (appropriate and continuous supply). + One-year data exclusivity, provided that the product meets an UMN. + Six-month data exclusivity for comparative clinical trials.
Antimicrobial resistance	Transferable data exclusivity voucher + one-year data exclusivity.
Environment	Increased environmental risk assessment requirements by adding environmental risk assessment for manufacturing and increasing the conditions of use of products to limit their environmental impact. Inclusion of antimicrobial resistance aspects in good manufacturing practices to ensure a more holistic environmental risk assessment along the pharmaceutical lifecycle.
Security of supply chain	Notification in case of shortage and withdrawal.
	Public disclosure of state funding received.

These options show that in the future, the key concepts for pharmaceutical incentives will be launched in all national markets and, to a lesser extent, UMN.

Option C is the directorate general's preferred option because, according to the EC, it would better reach the objectives and would, by far, be the best option for patients and public health. It would also be a fair compromise between originators and generics: Option A is better for originators and option B is better for generics.

However, Option C would force companies to launch in all national markets within two years of marketing authorization to benefit from the same incentives as they currently do. This new condition may be unrealistic, depending on the definition to be given to launch.

Rumor is that the directorate general would consider a launch as a signed pricing and reimbursement agreement followed by a continued effective marketing for two years.

If true, the new condition indeed is unrealistic, especially for small companies that generally cannot afford an EU-wide launch as well as for companies developing orphan and advanced therapy medicinal products, for which not only the small and scattered patient population does not justify an EU-wide

launch but also national pricing and reimbursement decisions are even more challenging to obtain than for regular medicinal products.

In addition, in some EU member states, national pricing and reimbursement systems are such that decisions may not be obtained within two years of the marketing authorization, either by law or in practice. Those member states would thus have to amend their legislation or practice.

The good news is that the directorate general seems to have abandoned the idea of forcing companies to disclose research and development costs to benefit from the pharmaceutical incentives.

Interestingly, the conduct of comparative clinical trials is incentivized because those trials help public authorities making better informed reimbursement decisions and accelerate pricing and reimbursement decisions and thereby access to patients.

The European Commission expects that 40% of all new medicinal products will be eligible to this added data exclusivity, which seems quite low as comparative trials are typically necessary for demonstrating clinical added value for pricing and reimbursement purposes.

Common Measures

The directorate general proposes the following measures to reduce administrative burdens both for the companies and the regulatory authorities:

- Removal of the sunset clause and the renewal after five years;
- Reduction of notifiable variations; and
- More complementarity with medical and IVF device rules regarding risk benefits assessments, companies' responsibilities and joint scientific advice.

The following measures are designed to streamline and accelerate regulatory procedures:

- New environmental risk assessment requirements and procedures for genetically modified medicinal products;
- New concepts: adaptive clinical trials, real world data and electronic product information;
- Use of expert assessment teams and multiexpert inspections teams; and
- EU-wide centrally coordinated process offering early dialogue and more coordination among the European Medicines Agency committees but also among clinical trial, marketing authorization, health technology assessment bodies, and pricing and reimbursement authorities.

Revision of Orphan and Paediatric Legislation

Both the Orphan Regulation and the Paediatric Regulation complement the General Pharmaceutical Legislation by providing additional incentives/rewards to develop products for rare and pediatric diseases.

Again, this article does not explain in detail the scope and the reasons for the revision of the Orphan and Paediatric Legislation.

The main objectives are to increase research and development in particular for high unmet medicinal needs, or HUMN; to ensure availability and timely access to patients; to make the regulations better

fitted to technological and scientific advances; and to improve and facilitate regulatory procedures.

Like for the General Pharmaceutical Legislation, the directorate general proposes, for each regulation, several policy options and common measures. The options however focus on pharmaceutical incentives.

Orphan Regulation

Five options have been examined:

Option 1	Same orphan exclusivity as now: 10 years.
Option 2	No orphan exclusivity.
Option 3	Variable orphan exclusivity based on the characteristics of the product: eight years if the product meets an HUMN; six years if the product contains a new active substance; or five years for all other products. + Two-year orphan exclusivity, provided that the product is launched in all national markets or there is no return on investment.
Option 4	Variable orphan exclusivity based on the characteristics of the product: eight years if the product meets an HUMN; six years if the product contains a new active substance; or five years for all other products. + New incentive (transferable priority review voucher), provided that the product meets a HUMN.
Option 5	New incentive (transferable priority review voucher), provided that the product meets a HUMN.

The European Commission's preferred option is Option 3 because, according to the European Commission, it would increase the number of orphan products while setting a more balanced orphan exclusivity system.

Moreover, this option does not include transferable vouchers, which the directorate general does not support because they would benefit more their buyers than the actual developers. Option C would also redirect investments to HUMN.

Indeed, under Option C, the current pharmaceutical incentive — 10 years orphan exclusivity — would be limited reduced to orphan medicinal products that meet a HUMD and are launched in all national markets.

Yet, the expectation is that no more than 30% of orphan products will meet the criteria for HUMN. Therefore, most orphan products would in fact benefit from eight-year orphan exclusivity, subject however to an EU-wide launch.

Of note, it is surprising that the European Commission proposes using the criterion of no return on investment since the studies on the Orphan Regulation conducted in view of the revision have shown that this criterion, which already exists in the current system, has basically not been used in 20 years.

The proposed common measures are the following:

- Criteria for HUMN;
- Increased scientific support from the European Medicines Agency if the product concerns an HUMN; in other words, a priority medicines, or PRIME scheme,[13] would be adopted;
- Transfer rather than withdrawal of the marketing authorization if the company loses interest in the product to promote continuous access like it is already the case for pediatric products;
- Duration of orphan designation capped at seven years. The objective is to force companies to accelerate the development of orphan products;
- Cumulative prevalence for different orphan conditions. Thus, an orphan product which generates sufficient revenues based on a first orphan designation, would generally not benefit from additional orphan incentives based on subsequent orphan designations. This restriction de facto pushes companies in investing either in one rare disease or in two or three rare diseases with, each, a very low prevalence;
- More flexible criteria to define orphan conditions;
- Decisions by the European Medicines Agency rather than the European Commission; and
- Streamline procedures. There will more cooperation and coordination among the European Medicines Agency, the health technology assessment authorities and the payers. Moreover, regulatory burdens would be reduced for generics and biosimilars.

Paediatric Regulation

Five options have also been examined:

Option 1	No reward
Option 2	Same rewards as now: six-month supplementary protection certificate, or SPC, extension or, for orphan products, two-year orphan exclusivity extension.
Option 3	Six-months SPC extension, provided that the product meets an UMN.
Option 4	Six-month SPC extension. + New reward if the product meets an UMN. The directorate general still hesitates among more months of SPC extension; or a transferable priority review voucher; or a transferable data exclusivity voucher.
Option 5	Extra prolongation of the SPC (i.e., more than six months) or a transferable priority review voucher or a transferable data exclusivity voucher (the directorate general still hesitates), provided that the product meets an UMN.

The proposed common measures are the following:

- Criteria for UMN;
- If the product concerns an UMN, increased scientific support from European Medicines Agency — i.e., a PRIME scheme — and research funding;

- Streamline the pediatric investigation plan procedure — for example: dynamic pediatric investigation plan, or simplified pediatric investigation plan for pediatric-use marketing authorization;
- Duration of deferrals capped to five years. This measure, which is supported by academics and patients, seems unrealistic, especially for rare diseases; and

- Adaptation of the waiver system to the mechanism of action. This already applies de facto to a few categories of products such as oncology products.

Overall, the changes brought by the common measures would bring the EU regime closer to the U.S. regime, which the industry considers a benefit given the increasing global development of medicinal products.

Coherence Between the Two Revisions Regarding Pharmaceutical Incentives

Annex 6 of the impact assessment for the revision of the General Pharmaceutical Legislation explains the coherence between the two revisions.

- Both revisions adjust the system of pharmaceutical incentives to a modulated approach, versus a one-size-fits-all approach.
- The key concepts are unmet medical need and accessibility for all EU patients.
- The General Pharmaceutical Legislation will define UMN, while the Orphan and Paediatric Legislation will define HUMN based on criteria related to disease and product, existence of already authorized products.

The impact assessments stress that the incentives would be combined. This, of course, is welcome.

However, assuming that the European Commission's current preferred options are adopted, companies would benefit from less incentives than they currently do unless they are launched in all national markets within two years from marketing authorization, including for orphan medicinal products, and such a launch is very unlikely, especially for orphan products.

Indeed, for medicinal products containing a new active substance, the European Commission's current preferred option would result in maintaining the current pharmaceutical incentives — eight-year data exclusivity followed by two or three-year marketing protection — but conditioning them to an EU-wide launch.

New data exclusivities, i.e., one-year in case the product meets an UMN and six-months in case comparative clinical trials are conducted, would become available, provided, however, that they apply independently of the basic eight-year protection, which is doubtful, and that, in the case of the one-year data exclusivity, the product meets the criteria for UMN, which will rarely be the case.

The outcome would be equivalent for orphan medicinal products since the 10-year orphan exclusivity would be reduced to eight years if the product meets an HUMN, six years if the product contains a new active substance or five years for all other products.

Given that only 30% of the future orphan products are expected to meet a HUMN, the orphan exclusivity would be reduced by four or five years for most orphan products.[14] Two additional years of orphan exclusivity would be available but, again, conditioned to an EU-wide launch of the product.

Conclusion

It is unclear if the European Commission will modify the proposed options with its preferences. The opportunity to amend the preferred options during the legislative process is clearer, which could lead to a reduction of pharmaceutical incentives if the link among all the measures is not maintained and the balance among the interest of all stakeholders is disputed.

Under the European Commission's current preferred options, the current pharmaceutical incentives for all medicinal products would be maintained, provided that the product is launched in all national markets but increased by one additional year of data exclusivity if, in addition, the product also meets an UMN. Orphan exclusivity would be reduced except for products that meet an HUMN and are launched in all markets.

While meeting an UMN or, for orphan products, an HUMN would become key for pharmaceutical incentives, it would be even the more so for an EU-wide launch.

However, companies decide not to launch a product in one or more member states for economic reasons, e.g. due to:

- The size of the target population which does not justify the costs of seeking pricing and/or reimbursement and of maintaining a separate label and product information; and

- The national pricing and reimbursement system which only allows for a low price and thereby triggers low prices in other countries as well, including outside the EU, due to international reference pricing.

Moreover, national pricing and reimbursement systems are currently such that, in some member states, decisions may not — by law or in practice — be obtained in two years.

In each impact assessment, the European Commission stresses the respect of the member states' exclusive competences regarding pricing and reimbursement, healthcare and the tax system.

Yet, the disconnect between, on the one hand, the EU Legislature that adopts the rules and imposes an always increasing number of expensive obligations, and, on the other hand, the member states that decide on pricing and reimbursement, creates market disfunction.

Revisions therefore will only be successful if they are fully supported by the member states through appropriate pricing and reimbursement of medicinal products. This is even more so if the launch of the product in all national markets becomes mandatory for benefiting from pharmaceutical incentive.

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[1] Communication from the Commission to the European Parliament, the Council, the European

Economic and Social Committee and the Committee of the Regions "Pharmaceutical Strategy for Europe", 25 Nov. 2020.

[2] Commission Decision of 16 September 2021 establishing the Health Emergency Preparedness and Response Authority.

[3] Proposal for a regulation of the European Parliament and of the Council on the European Health Data Space, 3 May 2022. The objective is to improve people' access to and control of their electronic personal data (primary use) and to facilitate the re-use of those personal data for public health across the EU (secondary use). The legislation would set out rules, infrastructure, and governance mechanism for those uses, ensuring data privacy and cybersecurity.

[4] Proposal for a regulation of the European Parliament and of the Council on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC, 14 July 2022.

[5] Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004,13 Nov. 2007.

[6] Revision of the EU general pharmaceuticals legislation roadmap https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Revision-of-the-EU-general-pharmaceuticals-legislation_en and Medicines for children & rare diseases — updated rules roadmap https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en.

[7] Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use, 6 Nov. 2001.

[8] Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, 31 March 2004.

[9] Antimicrobial resistanceproposals would be combined with other supports which are discussed as part of R&D and crisis preparedness policies.

[10] An additional year of marketing protection is granted if within the data exclusivity period, one or more therapeutic indications are approved that are considered [by the European Medicines Agency] as bringing a significant clinical benefit in comparison to existing therapies.

[11] "Data exclusivity" means that generic companies may not refer to the MA dossier of the innovative product in order to support their MA applications, and "marketing protection" means that generic companies may not place generic products on the market.

[12] Currently, an environmental risk assessment is required for all new MA applications. Potential risks from medicinal products to the environment are assessed by regulators and precautionary measures are taken by companies.

[13] A PRIME designation is the closest equivalent to the U.S. breakthrough designation.

[14] Companies would also lose the "de facto" 1 year protection arising from the fact that MA applications for generics and biosimilars may only be submitted after expiration of the orphan exclusivity period since, following the Revisions, those applications would be submitted earlier.