Comment by the Institute for Quality and Efficiency in Health Care of 7 June 2023 on the European Commission's Proposal of 26 April 2023 on the Reform of the EU Pharmaceutical Legislation[1]

12 June 2023

Promoting a robust evidence base for decision-making in national health care systems

A key objective of the European Commission's Proposal on the Reform of the EU Pharmaceutical Legislation (in short: "the Proposal") is to improve access to innovative drugs at the national level throughout the EU. The starting point is, on the one hand, the observation that, depending on the drug, there are currently considerable differences in access between countries, and, on the other, that drug development has so far only been geared to a limited extent towards the actual needs of patients ("unmet medical need"). This is in line with the perspective of the health care system, according to which a new drug is innovative if it improves health care, i.e. has an added value for patients compared to existing treatment options.

The EU Regulation on European health technology assessment (HTA Regulation), which came into force in January 2022, also aims to improve access to drugs with added value (added benefit) at the national level, and the Proposal therefore makes several references to the HTA Regulation.

It is a requirement that the new EU pharmaceutical legislation therefore also promotes and demands drug development that answers the questions of national health systems about the added benefit of drugs, and not only enables marketing authorization (MA) at the European level. Although the Proposal attempts to meet this requirement in some places, it does not do so overall for a number of reasons.

Market exclusivity period in the case of comparative studies: extend the duration, extend the evaluation criterion

The suggestion to also make the duration of market exclusivity dependent on the quality of the evidence submitted (comparative studies) is to be welcomed in principle. However, the planned 6-month extension for conducting comparative studies is far too short (e.g. only 5% of a total 10-year market exclusivity period). In IQWiG's view, it is necessary to extend the extension to 2 years and in return, for example, to shorten the currently planned basic period of 6 years accordingly.

Irrespective of this, the evaluation criterion contained in the Proposal that comparative studies are part of the MA dossier should be expanded: From the perspective of the health care system, it is sufficient (and also necessary) that the results of comparative studies are available at the time of or shortly after market access. In addition, comparative studies not included in the MA dossier but already started should also allow extension of market exclusivity, provided that recruitment was completed prior to MA and that the study results

[1] Translation of the German document "Stellungnahme des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen vom 07.06.2023 zum Legislativvorschlag zur Revision des EU-Arzneimittelrechts der Europäischen Kommission vom 26.04.2023"

are already available or planned to be available at the latest one year after MA, i.e. shortly after the expected market access. In the latter case, the decision on the extension of market exclusivity should be confirmed or revoked upon study completion, depending on adherence to the schedule. An example is the study programme for osimertinib in lung cancer: MA was based primarily on non-comparative studies that were not suitable for addressing the question of added benefit [1]. However, because a comparative study had been conducted in parallel with the MA procedure, the results were available soon after market entry, and a follow-up assessment was performed to answer the question of the added benefit of osimertinib [2].

Provision of excellent data and research infrastructure necessary at the EU level

In the future it will also only be possible to identify real progress in drug therapy using high-quality evidence. And only then will it be possible, through faster access and/or financial incentives, to prioritize the uptake of drug innovations that represent real therapeutic progress into national health care systems across Europe, thus achieving one of the main objectives of the reform of EU pharmaceutical legislation. The subject of the reform must therefore be not only to incentivize the generation of high-quality evidence, but also to reduce the hurdles in this regard.

In this context, the experiences of the COVID 19 pandemic should also be considered: The major advances in the field of drugs and vaccines were achieved through pragmatic randomized controlled trials (RCTs) with short preparation periods. These include not only the large phase III studies on vaccine development, but also platform studies comparing several treatment options. Of particular note is the RECOVERY study conducted in the United Kingdom, which at the early stage of the pandemic showed a survival benefit for dexamethasone in severely ill patients [3]. Other examples include the PRINCIPLE study in the outpatient setting [4] and the TOGETHER study of repurposed drugs [5].

Excellent drug research in Europe can therefore be particularly successful if a data and research infrastructure is established that allows high-quality studies, including interventional studies, to be conducted quickly and with few obstacles. Such an infrastructure also includes the provision of resources for the planning, management and analysis of studies, which will support drug development by small and medium-sized enterprises (SMEs) and non-profit organizations as well as facilitate the conduct of platform studies comparing several drugs, as they could be managed centrally.

In particular, drug development in small populations (e.g. rare diseases, paediatrics) will also benefit from a data and research infrastructure that enables development programmes with efficient adaptive study designs (the above-mentioned platform studies). Such studies are therefore explicitly mentioned in the Proposal.

However, besides unresolved issues such as the quality of data from heterogeneous sources, the structures currently envisaged (European Health Data Space [EHDS] including DARWIN) explicitly exclude interventional studies, and thus also pragmatic RCTs. An essential branch of excellent research with data collected in routine practice ("real world data") is therefore currently prevented in these structures, which contradicts an objective of the reform of the EU pharmaceutical legislation, namely, to take account of technological advances in the

generation and evaluation of health data. As a result, the EU is also losing touch with the international research landscape, not only at the academic, but also at the regulatory level, as the US Food and Drug Administration (FDA), for example, specifically considers pragmatic RCTs with "real world data" [6]. The reform of the EU pharmaceutical legislation provides the opportunity (but also the necessity) to undertake countermeasures here.

The establishment of an excellent data and research infrastructure as described above should be linked to the mandatory conduct of MA studies in the EU within this structure, wherever reasonable and possible. Alternatively, the use of the infrastructure should be established as a component of variable market exclusivity periods. Ideally, and particularly for rare diseases and paediatrics, this should take place in the form of efficient platform studies. In addition to the pragmatic RCTs already mentioned, this use of an excellent data and research infrastructure on the one hand also allows long-term follow-up after the actual MA study has been completed, regardless of whether it was a comparative or non-comparative study. On the other, the consistent use of such an infrastructure reduces major hurdles regarding the interpretability of non-randomized comparative studies. This is because when different data sources are used for the new drug (single-arm MA study) and the comparator therapy (e.g. real world data), as is often the case nowadays, in addition to methodological challenges, there are sometimes insurmountable hurdles due to insufficient interoperability as well as considerable differences in data quality and availability between the different data sources.

Determining an evidence-based comparator: involvement of HTA agencies required

According to the Proposal, comparative studies should only lead to an extension of market exclusivity if they are conducted with an evidence-based comparator. Although this makes sense in principle, the procedure to determine an evidence-based comparator described in the Proposal is inappropriate.

According to the Proposal, determining this comparator should result from advice given by the EMA to the pharmaceutical company. However, the question of evidence-based comparators falls within the competence of the national HTA agencies and is hence incorporated in the HTA Regulation, e.g. in the context of the definition of national research questions following the PICO scheme. It is therefore necessary that the competence of the HTA agencies is used to determine an evidence-based comparator, e.g. in the context of joint consultations with the EMA, which are also envisaged in the HTA Regulation.

Supporting the development of drugs for special therapeutic indications, in particular rare diseases

It is in general understandable and reasonable to undertake measures to support drug development in areas of high medical need. These include many rare diseases for which no (or no satisfactory) treatment options exist. However, as stated in the general objectives of the Proposal, for rare diseases too, drug development should be encouraged that offers real added value for patients, and these drugs should then be made available throughout the EU. For rare diseases, the Proposal does not meet these objectives.

Abolishment of the criterion “significant benefit” required

The Proposal envisages some adjustments in relation to the granting of orphan drug status. However, the criterion "significant benefit" is to remain largely unchanged. This means that in cases where a satisfactory method of diagnosis, prevention or treatment already exists, a new drug for a rare disease can be granted orphan drug status if it is considered to be of “significant benefit”.

However, it has been empirically proven that the criterion "significant benefit" does not reflect the actual state of evidence in terms of added benefit compared to the standard of care [7]. This criterion should therefore be abolished, also because granting orphan drug status on the basis of this criterion can have far-reaching consequences for national reimbursement decisions [8]. Maintaining this criterion jeopardizes the aim of the reform, which is to ensure the uptake in particular of those drugs in health care systems in Europe that have a proven added value for patients.

Incentives for high-quality evidence and EU-wide market access should also be set for rare diseases and other therapeutic indications to be promoted

The fact that around half of orphan drugs have no proven added benefit over the existing standard of care is in most cases caused by the lack of adequate comparative data [7]. Supporting orphan drug development, as still envisaged in the Proposal, will therefore need to adequately consider the component of evidence generation in order to be successful.

This includes not only the provision of an excellent data and research infrastructure, as described above, but also incentives to conduct comparative studies, which are currently not planned. In addition, as EU-wide access is currently insufficient, especially for orphan drugs, and is therefore a key objective of the reform, this component is also important in determining the duration of market exclusivity, but is also currently not envisaged.

Overall, it therefore seems reasonable not to apply special rules to orphan drugs, but in principle to apply the general rules for determining the duration of market exclusivity. In this context, separate support for orphan drugs can be made possible by an additional component, e.g. by extending market exclusivity by one year.

This additional component could also be generally applied to the treatments or therapeutic indications to be promoted, thus also addressing, for example, the intended support for the development of paediatric drugs and reserve antibiotics. Overall, such a fundamental standardization of the rules for determining the duration of market exclusivity would be linked to the fact that both the generation of high quality evidence and EU-wide access would be supported in principle, thus addressing two of the main objectives of the Proposal for each therapeutic indication.

Definition of the criterion “unmet medical need”

The criterion "unmet medical need" plays a central role in the Proposal. For example, in the section on reasons for the Proposal it is mentioned that drug development in the EU should in future focus more on "unmet medical needs", which, according to the EU Commission, has

so far only been the case to a limited extent. However, the term "unmet medical need" also has a specific meaning, e.g. in determining the duration of market exclusivity for a new drug.

In IQWiG's view, the basic definition in the Proposal is reasonable (“a life-threatening or seriously debilitating disease with remaining high morbidity or mortality, and the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality”). However, the suggestion for implementation is insufficient, in particular for the following reasons

- The component “remaining high morbidity and mortality” is only to be specified in later “implementing acts”.

- Information is lacking on how the component “the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality” is to be specified. This requires high quality comparative data, which are not necessarily envisaged in the MA procedure. In addition, the determination of a "meaningful reduction" depends on the baseline situation and thus on current health care, including treatments already available. In cases where treatment options already authorized are not available throughout the EU, a uniform statement on the question of "meaningful reduction" is therefore neither reasonable nor possible. It remains unclear which approach should be followed in the European Commission’s view (e.g. theoretically best possible care in the EU or average standard of care in the EU).

Overall, due to the far-reaching consequences of the term "unmet medical need", IQWiG believes that it is necessary that the criteria for demonstrating unmet medical need are clearly defined in the Directive itself and not, as currently envisaged, in subsequent implementing acts. The path of scientific substantiation suggested in the Proposal should involve representatives of national health systems and HTA agencies.

Transmission of individual patient data to the EMA

The Proposal includes the transfer of individual patient data (IPD) to the EMA, an approach we fully welcome. The long-standing practice of the FDA, which regularly uses IPD for its own analyses, shows that this can provide important insights beyond the MA dossier and any additional analyses by the pharmaceutical company.

However, the targeted analysis of IPD is not only of great importance for the MA procedure of the EMA, but also for the upcoming EU HTA assessments. After providing justification, European HTA agencies should therefore be given access to the IPD available to the EMA. In this context, the EMA should make two types of data available:

- as IPD, provided that a relevant risk of re-identification can be excluded for patients
- as an aggregated analysis prepared by the EMA regarding the question submitted by the HTA agency.

Likewise, after providing justification, pharmaceutical companies should be given access to IPD from studies conducted by other sponsors if this is required in the context of the EU HTA procedure. This may be the case, for example, when generating indirect comparisons for the EU dossier.

MA applications based on bibliographic data: evidence-based approach required

Like the current EU pharmaceutical legislation, the Proposal envisages the possibility of an MA application based on bibliographic data. Such applications make use of publicly available information. It has been shown several times that this type of information may result in a markedly biased picture due to selective data publication (entire studies, but also individual study data) [9, 10]. In IQWiG's view, it is therefore necessary that MA applications based on bibliographic data and the related MA decisions follow the standards of evidence-based medicine. In particular, this includes the following aspects:

- To avoid selective data submission, the data in the MA dossier must be based on a systematic review.
- Extensive information retrieval must represent an essential part of the systematic review, not only to identify all publicly available information on completed studies, but also to identify previously unpublished studies.
- The potential impact of unpublished data (entire studies, individual results) must be taken into account in the MA decision.

These requirements for the MA dossier and for the assessment by the regulatory authorities should be laid down in implementing acts, and should be incorporated into the reform of the EU pharmaceutical legislation.

Comparative advertising claims: reference to summary of product characteristics not reasonable

The Proposal contains various rules for the advertising of prescription drugs. In principle, comparative advertising claims are to be prohibited, unless the summary of product characteristics (SmPC) of the advertised drug contains comparative statements.

In IQWiG's view, this exception is not reasonable for the following reasons in particular:

- In SmPCs, studies and their results are presented in a highly abbreviated form. This presentation is therefore often incomplete or partially biased (see e.g. [11, 12]) and, in the case of indirect comparisons, often methodologically problematical.
- Comparative assessments are the responsibility of HTA agencies, e.g. within the framework of the future EU HTA. However, the assessments by HTA agencies are not considered in the SmPC, leading to potential contradictions between advertising claims and conclusions in HTA reports.

In summary, the exception regarding the use of comparative claims from the SmPC for advertising purposes should therefore be abolished.

Cologne, Germany, 7 June 2023

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