Proposal for amendments
by the German Medical Association and the
Drug Commission of the German Medical Association

EU legislative proposals COM(2023)192 and 193 on medicinal products

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Preliminary Remarks

The following statement has been prepared by the German Medical Association and the Drug Commission of the German Medical Profession (DCGMA). For the sake of readability, we are addressing the Directive and the Regulation proposals in one document. Proposed amendments to the Directive are marked in blue, while proposed amendments to the Regulation are marked in red. The amendments suggested should not be considered exhaustive. As our analysis of the proposals is a work in progress, further suggestions for amendments may be presented at a later stage.

1. Review of the incentive framework: Data and market protection / accelerated market access for generics

The Commission has proposed a general review of the rules granting data and market protection for newly developed medicinal products. The basic data protection period would be reduced from 8 to 6 years, with an additional 2 years of market protection (during which a generic medicine may already be developed).

According to the Commission´s proposal, extensions of the data protection period apply if additional conditions are fulfilled, namely:

- 24 months if the product is brought, or offered, to the market in all 27 Member States (Art. 81 (2) a) Directive);
- 6 months if the medicinal product addresses an unmet medical need (Art. 81 (2) b) Directive);
- 6 months if the developer carries out comparative clinical trials for a product containing a new active substance (Art. 81 (2) c) Directive);
- 12 months if authorisation for (a) further therapeutic indication(s) is obtained after marketing authorisation and during the data protection period (Art. 81 (2) d) Directive).

For orphan drugs, a market exclusivity period of 9 years shall apply as a baseline scenario, with the following possible extensions:

- 12 months if the product is brought to the market in all 27 member states, or offered to all member states (Art. 72 (1) Regulation);
- 12 months if the medicinal product addresses an unmet medical need (Art. 70, 71 (2) b) Regulation);
- 12 months if authorisation for a further therapeutic indication is obtained after marketing authorisation; this extension can be used for a maximum of two new indications (Art. 72 (2) Regulation).

Hence, if all conditions are fulfilled, the maximum duration of marketing protection (12 years / 13 years for orphan drugs) would exceed the current maximum of 10 years.

The Commission hopes that reducing the data protection period in the baseline scenario (in combination with other measures, such as including the “Bolar exemption” in Art. 85 Directive) will help to achieve accelerated market access for generics, leading to an increase

in competition and a decrease in prices, while at the same time incentivising research and market behaviour which can improve patient access to innovative medicines.

The German Medical Association and the DCGMA support, in general, reducing the data protection period from 8 to 6 years in the baseline scenario, and the possibility to extend protection if the above-mentioned additional conditions are fulfilled.

→ However, we suggest that the extensions mentioned in Art. 81 (2) Directive be given to the market protection, not to the data protection period. This would require amending Art. 81 (2) and Art. 82 (1) and (3) Directive.

This would grant the original marketing authorisation holder the same duration of protection from competitors and planning reliability but would enable a developer of a generic or biosimilar to start developing their product earlier, encouraging an earlier market entry.

Moreover, we advise capping the maximum duration of the protection period to 10 years. Allowing a protection period which exceeds the current protection/market exclusivity periods would thwart the objective of the proposed revision to allow for earlier market entry of generic drugs.

→ We suggest adding a paragraph to Art. 81 Directive:

> *"The cumulative duration of the data and market protection period for a medicinal product shall not exceed ten years from the date the initial marketing authorisation was granted."*

Such a cap had been included in the leaked draft Directive proposal of January 2023.

2. Introduction of transferable exclusivity extension vouchers

The German Medical Association and the DCGMA believe that market-based incentives like "transferable exclusivity extension vouchers" (TEEV, Art. 40 – 42 Regulation) risk over-compensating manufacturers of already-profitable medicines at the expense of health systems, and risk becoming a gambling tool which should be avoided.

While we support the approach of decoupling the size of the incentive from the quantity of the priority antimicrobial sold, we would favour an incentive mechanism which remains more predictable for public budgets. These include models in which countries (or the EU, for example) guarantee a certain amount of income for the right to be supplied a priority antimicrobial ("subscription model" or "Netflix model"). Another option would be an agreed upon incentive for a defined target, e.g., the market entry of a priority antimicrobial.

We acknowledge that such mechanisms would have to be decided and implemented through means other than EU legislation. However, this also means that work could already start before the proposed revision of the EU pharma legislation is adopted and effective, which

would give the mechanism a timely edge over TEEV. We believe that HERA should be involved in the development and implementation of such an incentive.

Apart from the above-mentioned reservations, if the EU legislator should decide to introduce TEEVs, such an incentive should be designed in a way to prevent abuse. We see a risk of abuse of the TEEV incentive if the marketing authorisation holder (MAH), after selling the TEEV to another party, ceases to fulfil the request for supplying, procurement, or purchasing of the priority antimicrobial in the European Union. In such case, it must remain possible for the Commission to revoke the TEEV. However, Art. 42 (2) states that a TEEV can only be revoked prior to its transfer.

An extension of exclusivity, whichever party benefits from it, is justified only as long as the priority antimicrobial actually remains available. Consequently, if the holder of the marketing authorisation that has benefited from a TEEV fails to ensure sufficient supply, the TEEV should become invalid irrespective of who is using it. To protect the buyer from damage resulting from a possible revocation of a voucher after the transfer, seller and buyer can make contractual liability arrangements.

→ We suggest deleting the words *"prior to its transfer"* in Art. 42 (2) Regulation.

A priority antimicrobial benefitting from a specific incentive should always be considered a "critical medicinal product" so that pursuant to Art. 127 Regulation, its supply will be monitored at European level. In case of an intended withdrawal of the marketing authorisation by the MAH, the product can continue to be produced and supplied by another interested party (Art. 24 (4) Regulation).

To ensure that priority antimicrobials will be reserved for human use only, they should also be added to the European Commission's list of antimicrobials reserved for use in humans, according to Implementing Regulation (EU) 2022/1255 of 19 July 2022.

→ We suggest adding a paragraph (4a) to Art. 40 Regulation:

> *"A priority antimicrobial shall be considered a critical medicinal product in the sense of Art. 2 (13).*
> *The Commission shall include priority antimicrobials in the list of antimicrobials reserved for treatment of certain infections in humans in accordance with the Regulation (EU) 2019/6 of the European Parliament and of the Council."*

In addition to strict stewardship rules, any incentive for the development of priority antimicrobials would have to be supplemented by rules or agreements effectively limiting the use of a priority antimicrobial in non-EU countries in a similar way, ideally at the WHO or G20 level.

3. Limiting unnecessary use of antimicrobials

The proposed Directive contains several provisions designed to limit the use of antimicrobials to what is strictly necessary:

- Applications for marketing authorisation for antimicrobials should contain an assessment of the risk of antimicrobial selection (Art. 22 (4) Directive) caused by the release of the antimicrobial substances into the environment through manufacturing and supply, use and disposal of the product in the EU and third countries.
- Applications for marketing authorisation must also contain an antimicrobial stewardship plan. The competent authority can impose additional obligations if it considers the risk mitigation measures contained in the stewardship plan insufficient (Art. 17 Directive).
- Antimicrobials should become prescription-only medicines throughout the EU (Art. 51 (1) (e) Directive).
- MAHs will be obliged to ensure the availability of educational material for health professionals on diagnostics relating to antimicrobial-resistant pathogens (Art. 69 (1) Directive).
- The packaging of antimicrobial medicines should contain a separate awareness card for users (Art. 69 (2) Directive).
- MAHs shall ensure that the package size corresponds to the usual dosage and duration of treatment (Art. 17 (3) Directive).
- Member States may set additional conditions for the prescription of antimicrobials, limit the validity of prescriptions and the quantity prescribed to what is necessary for the treatment concerned (Art. 51 (2) Directive).

The German Medical Association and the DCGMA agree with the provisions on containment of antimicrobial resistance (AMR). As we believe that fighting antimicrobial resistance requires a comprehensive approach, we welcome that the Commission's proposal addresses several stages in the product life cycle of medicines, both involving developers and manufacturers and relying on the responsibility of patients and healthcare professionals.

While it is important that healthcare professionals be adequately informed about the proper use of antimicrobials, providing this information should generally be the competent authorities', and not the MAH's responsibility. Neither would it be appropriate to entrust sales representatives with this task. It must be ensured that the information on the appropriate use of the diagnostic tools is compatible with the summary of product characteristics and does not involve advertising.

→ We therefore suggest amending Art. 69 Directive as follows:

*"In case of absence of appropriate guidelines, T*the *marketing authorisation holder shall ensure availability of educational information material to healthcare professionals, including through medical sales representatives as referred to in Article 175(1), point (c), regarding the appropriate use of diagnostic tools, testing or other diagnostic approaches related to antimicrobial-resistant pathogens, that may inform on the use of the antimicrobial.*
The informational material referred to in the first paragraph shall be compatible with the summary of product characteristics.

Materials referred to in the first subparagraph shall not constitute advertising referred to in Chapter XIII."

Despite the need to limit the unnecessary use of antibiotics in human medicine, the proposals should not interfere with the professional assessment of physicians as to which individual cases justify the (immediate) administration of an antibiotic. Diagnostic tests may be a very useful tool and even if their potential is not yet fully exploited, it may be justified to prescribe antimicrobials without prior diagnostic tests taking into account the urgency and the individual situation of the patient.

→ We therefore suggest the following deletion in Recital (68) of the Directive:

"While this Directive restricts the use of antimicrobials by setting certain categories of antimicrobials under prescription status, due to the growing antimicrobial resistance in the Union, competent authorities of the Member States should consider further measures for example expanding the prescription status of antimicrobials ~~or the mandatory use of diagnostic tests before prescription~~. Competent authorities of the Member States should consider such further measures according to the level of antimicrobial resistance in their territory and the needs of patients."

4. Pricing policy and price transparency

The Commission proposes that MAHs be required to publicly disclose financial support from public or publicly financed sources (Art. 57 Directive).

The German Medical Association and the DCGMA support transparency obligations, as disclosure of financial support and the research and development costs helps to assess the justification of the prices requested by MAHs. To provide a more complete picture,

→ we suggest rephrasing Art. 57 (1) and (2) a) Directive as follows:

"Responsibility to report on public financial support

1.The marketing authorisation holder shall declare to the public any direct financial support and indirect financial benefits received from any public authority or publicly funded body, in relation to any activities for the research and development of the medicinal product covered by a national or a centralised marketing authorisation, irrespective of the legal entity that received that support.

2.Within 30 days after the marketing authorisation is granted the marketing authorisation holder shall:

(a) draw up an electronic report listing:

(i) the amount of financial support received and the date thereof;
(ii) the public authority or publicly funded body that provided the financial support referred to in point (i);
(iii) the legal entity that received the support referred to in point (i).
(iv) the total research and development costs related to the medicinal product."

5. Repurposing of medicines

The Commission has proposed that not-for-profit entities may submit documentation containing evidence on a new indication of an authorised medicinal product to the EMA or national competent authorities (Art. 48 Regulation). In the case of an unmet medical need, the EMA can undertake further examinations and publish an opinion. MAHs may be required to adapt their product information.

If the marketing authorisation is extended by an additional indication and if this constitutes a significant clinical benefit supported by clinical studies, four years of data protection will be granted if the medicinal product in question has not yet benefited from data protection (Art. 84 Directive).

The German Medical Association and the DCGMA support the proposal which would enable regulatory authorities to modify marketing authorisations at their own initiative, based on scientific evidence.

6. Preventing and managing shortages

Duty to ensure appropriate and continued supplies (Art.56 (3) Directive):

Marketing authorisation holders' obligation to ensure appropriate and continued supplies is at the centre of the Commission's stated intention to improve availability of medicines for patients. Ensuring appropriate supplies is a key responsibility of MAHs, and typically within their power. This is not altered by the fact that there may be exceptional events beyond MAHs' control, like *force majeure*, for which a MAH cannot and should not be held liable.

However, narrowing down the MAH's obligation from the outset to "*the limits of its responsibilities*" without providing a proper definition of these responsibilities seems like an invitation to evade the obligation to ensure appropriate and continued supplies and risks rendering Art. 56 (3) Directive completely toothless.

To provide for a real improvement to the current situation, there needs to be a possibility to sanction severe and repeated violations of the obligation in Art. 56 (3) Directive. Art. 172 (1) Regulation provides for the possibility of the Commission to impose financial penalties for non-compliance of MAHs.

→ We suggest amending Art. 56 (3) Directive as follows:

> *"The marketing authorisation holder of a medicinal product placed on the market in a Member State shall~~, within the limits of its responsibility,~~ ensure appropriate and continued supplies of that medicinal product to wholesale distributors, pharmacies or persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered. The arrangements for implementing the first subparagraph should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the*

Treaty rules, particularly those concerning the free movement of goods and competition."

→ Moreover, we suggest including in Annex II of the Regulation the obligation to ensure appropriate and continued supplies, referred to in Art. 56 (3) Directive.

Extended notification obligations (Art. 116 Regulation):

The Commission has proposed that MAH should notify the intention to permanently withdraw a medicine from the market at least 12 months before the last supply in the Member State concerned (Art. 116 (1) a) + b)). The same applies if the MAH permanently does not have sufficient quantities of the respective product to cover the demand. Temporary discontinuations or interruptions of supply lasting more than 2 weeks shall be notified at least 6 months in advance (Art. 116 (1) c)).

The establishment of an early warning mechanism for shortages of urgently needed medicines beyond health emergencies and "major events" for medicines supply within the meaning of Regulation (EU) 2022/123 corresponds to a demand of the German Medical Association and the DCGMA. Likewise, the envisaged 6-month period for notification in the case of temporary interruption of supplies and the 12-month period in the case of permanent discontinuation is supported. Parallel notification and information systems at EU and (sub-) national level should be avoided.

We are pleased to note that Art. 172 (1) and Annex II (10) Regulation provide for the possibility of penalties for MAHs' failure to comply with their obligation in Art. 16 (4) Regulation to provide information on the intended suspension or cessation of marketing and on potential or actual shortages. However, as the information mentioned in Art. 16 (4) goes beyond volumes of sales and prescriptions, we believe that a clarification in (10) Annex II is necessary:

→ We therefore suggest amending (10) of Annex II Regulation as follows:

"(10) the obligation to notify the Agency of the dates of actual marketing and of the date when the medicinal product for human use ceases to be on the market, and to provide to the Agency data relating to the volume of sales and the volume of prescriptions of the medicinal product for human use, and with the information ~~as~~ provided in Article 16(4);"

Monitoring of shortages (Art. 117 – 126 Regulation):

The Commission has proposed that MAHs shall submit a shortage prevention plan and, upon request, a shortage mitigation plan. The national competent authorities carry out continuous monitoring of impending or existing shortages for centrally authorised medicines in cooperation with the EMA (Art. 118 (1)). They publish supply shortages on their websites (Art. 121 (1)).

National authorities report to the EMA shortages that cannot be resolved at national level. The Steering Group on Shortages and Safety on Medicinal Products (MSSG) at the EMA decides which shortages require European coordination. These are included in a list of "critical shortages"; shortages are to be published when there is a recommendation for health professionals and patients on how to deal with them. The Steering Group (MSSG) can make recommendations on how to avoid and deal with the shortages; these are to be implemented by the Commission.

→ The inclusion in Annex II Regulation of the obligation to have in place and keep up to date a shortage prevention plan as provided for in Article 117, and the obligation to comply with the recommendations and measures taken in case of a critical shortage as provided for in Article 125, should be considered.

The German Medical Association and the DCGMA support the envisaged publication of shortages. Especially in cases of critical shortages where substitution with another readily available medicinal product is not possible, healthcare professionals require a timely recommendation by the EMA, to enable them to change treatments in time. The EMA should provide such recommendations for each critical shortage, and each critical shortage should be published.

→ Accordingly, we suggest inserting a new Art. 124 (2a) and making the following changes to Art. 124 (3) Regulation:

"(2a) The Agency shall assess actual critical shortages of medicinal products and provide recommendations to healthcare professionals and patients.

(3) The Agency shall establish within its web-portal referred to in Article 104 a publicly available webpage that provides information on actual critical shortages of medicinal products ~~in cases in which the Agency has assessed the shortage and has provided recommendations to healthcare professionals and patients~~. This webpage shall also provide references to the lists of actual shortages published by the competent authorities of the Member State pursuant to Article 121(1), point (b)."

We believe that healthcare professionals should be able to report shortages at their own initiative.

The obligation of manufacturers to ensure the traceability of the origin of the ingredients of medicines as well as the obligation to communicate this to the competent authorities upon request (Art. 58 Directive) is also welcomed.

Lastly, the German Medical Association and the DCGMA support the possibility for the European Commission to adopt measures in case of critical shortages (Art. 126 Regulation).

Specific rules for critical medicines (Art. 127-134 Regulation):

The Steering Group (MSSG) is to draw up a list of medicines of critical importance, publish it on the EMA web portal and keep it up to date, and monitor the supply of these medicines.

Based on recommendations of the Steering Group, the Commission should be able to take measures via implementing acts to improve the secure supply of these medicines, including stockpiling obligations for medicinal products to be imposed on MAHs, wholesalers, or other parties (Art. 132-134).

The German Medical Association and the DCGMA welcome the creation of an EU list of critical medicines whose availability is coordinated at EU level, and the introduction of stockpiling obligations. Stockpiling obligations are an essential component in ensuring more constant supplies of critical medicines. Building up contingency stocks requires proper preparation and lead time on the part of the MAHs. Therefore, stockpiling obligations should be introduced by the Regulation itself, and not by implementing acts on an *ad hoc* basis, as suggested by the Commission (Art. 134 (2)).

→ We suggest inserting a new Art. 128 (3) Regulation:

> *"The marketing authorisation holder as defined in Article 116(1) Regulation shall be responsible for setting up and maintaining minimal safety stocks of critical medicinal products referred to in Article 131.*
> *Minimal safety stocks of critical medicinal products shall be sufficient to meet the two-month demand for that critical medicinal product in those Member States where the medicinal product has been placed on the market.*
> *The marketing authorisation holder may submit a request to the competent authority concerned for an exemption from maintaining minimal safety stocks on the following grounds:*
>
> *(a) the manufacturing process or shelf life of the critical medicinal product is not compatible with the duration of the minimal safety stocks;*
>
> *(b) other valid reasons agreed with the competent authority concerned."*

→ In order to make these obligations effective in practice, the obligation to maintain safety stocks and the obligations mentioned in Art. 133 Regulation should be included in Annex II of the Regulation.

We consider that decentralised storage at manufacturers' sites is more appropriate than centralised European warehouses, as is being considered for measures against certain cross-border health emergencies. It should also be borne in mind that the establishment of reserves must take place with sufficient lead time to make sure that the creation of stocks does not provoke shortages in turn.

We clearly support the obligation to offer the transfer of the marketing authorisation to another interested party (Art. 24 (4) Regulation) where a MAH intends to stop the production of a critical medicine. However, we would like to point out that it remains unclear how "reasonable terms" are to be interpreted. Without the possibility of these terms being set by an independent body, this possibility risks running dry in practice or leading to frequent lawsuits.

7. Environmental aspects

For every medicinal product with an antimicrobial property, an assessment of the risk of its contribution to the spread of antimicrobial resistance along the entire product life cycle would be required (Art. 22 (4) Directive) in the environmental risk assessment (see above Section 3).

Medicinal products with potentially environmentally harmful properties which were authorised before 30 October 2005 and have therefore not yet been subject to an environmental risk assessment are to be examined in an EMA programme. The EMA is to present the programme 30 months after the Directive enters into force (Art. 23 Directive). The EMA, in cooperation with the Member States, shall establish an evaluation system for a knowledge database on the environmental properties of active substances used in authorised medicines that may pose a risk to the environment (Art. 16 Directive).

The German Medical Association and the DCGMA support increased requirements for the environmental impact assessment. We expressly agree with the inclusion of the risk of AMR proliferation. Furthermore, we support the proposed prescription requirement for environmentally harmful medicines.

8. Emergency marketing authorisations and compulsory licenses in health crisis situations

The German Medical Association and the DCGMA support temporary emergency marketing authorisations in health crisis situations for medicines needed for the prevention, diagnosis or treatment of a severe and/or life-threatening disease directly related to the health crisis (Art. 30, 31 Regulation).

We also support the possibility of granting compulsory licenses which suspend the data and market protection of the affected medicinal product in public health emergencies (Art. 80 (4) Directive).

→ We would welcome a clarification in Art. 23 Regulation that the granting of a temporary emergency marketing authorisation pursuant to Art. 30 shall leave the civil and criminal liability of the manufacturer and marketing authorisation holder unaffected.

The experience of redacted passages in contracts with vaccine manufacturers during the Covid-19 pandemic should be avoided in the future.

9. Product information

The Commission has proposed that Member States may replace package leaflets containing product information with an electronic format. Six and a half years after the Directive comes into force, the Commission would be empowered to prescribe the electronic form, providing

a qualified majority of Member States has allowed the electronic form. Patients should have the right to a printout of the information upon request (Art. 63 Directive).

The German Medical Association and the DCGMA suggest that the revision of the rules on product information be used to introduce a paragraph with the most important information (e.g., "key information section" or "drug facts box"). This should be done in the package leaflet in an easy-to-understand language for patients.

→ We suggest amending Art. 63 (3) Directive as follows:

"(3) ~~Member States may decide that t~~The package leaflet shall be made available in paper format ~~or~~ and electronically~~, or both~~. ~~In the absence of such specific rules in a Member State, a~~ A package leaflet in paper format shall be included in the packaging of a medicinal product. ~~If the package leaflet is only made available electronically, the patient's right to a printed copy of the package leaflet should be guaranteed upon request and free of charge and .~~ It should be ensured that the information in digital format is easily accessible to all patients."

Art. 63 (5) Directive should be deleted.

10. Regulatory support and flexibility

The extension of scientific support by the EMA for promising medicinal products for the treatment of diseases with unmet medical needs is an important approach to shortening approval times. The advisory support through accelerated assessment procedures (Art. 58 ff. Regulation; Art. 60 Regulation) also appears helpful.

The use of ongoing reviews to accelerate authorisation procedures (e.g., the rolling review procedure used for the conditional marketing authorisation of Covid-19 vaccines) for medicines with exceptional therapeutic progress in unmet medical needs (Recital (58) and Art. 19 Regulation) is useful but should only be applied restrictively due to the temporary lack of evidence.

Accelerating approval procedures and making them more flexible must not lead to lower standards for the evidence to be provided with regard to efficacy and safety, as this could result in an increased risk for patients. The use of "big data" or "real world data" should only be included under thorough scientific monitoring and evaluation.

Despite the restrictions envisaged, the positive and negative effects of "regulatory sandboxes" can hardly be assessed at present. We urge the European legislator to take a cautious approach.

11. Additional need for EU action: Coordination on criteria for public tenders

The German Medical Association and the DCGMA calls on the EU to counteract a (further) migration of pharmaceutical production from Europe to third countries and further market concentration, including non-patent-protected medicinal products. To this end, the EU pharma legislation should be supplemented by a recommendation of the European Commission on tender criteria for medicines that are not oriented towards the lowest price only.

In our view, appropriate criteria could be, for example:

- preference for medicines produced within the EU;
- consideration of European or equivalent occupational health and safety, social and environmental protection standards in the case of production in third countries, including measures to prevent the spread of AMR;
- diversification of production sites;
- reliability of suppliers in the past;
- awarding the contract to more than one applicant.

The Commission should meet regularly with the competent bodies of the Member States to exchange information on their experiences with tendering procedures, and monitor the application of the criteria and their impact on prices and availability of medicines.