Joint statement of NIHDI (Belgium) and the Netherlands, members of the Beneluxa Initiative

Joint approach towards EU consultation on pharmaceutical legislation revisions

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- **A holistic approach to pharmaceutical legislation**
  - Revision of EU pharmaceutical legislation requires a holistic approach not just analysing individual pieces of legislation, but also looking at gaps, overlaps and inefficiencies between different pieces of legislation, including the Clinical Trial Regulation and frameworks for GMOs, SoHO, ATMPs, IP, digitalisation etc. In addition, a holistic approach takes into account the impact of regulatory provisions and decisions on downstream actors such as HTA body and payers and eventually the patient. Trade-offs between one overarching legislation and separate legislation should be carefully weighed.

- **A shift from an applicant-driven to system that is also regulator/payer-driven system is essential**
  - Currently, pharmaceutical industry determines what data are submitted and when and where. However, there is also the need for a more patient-oriented approach, where regulators and payers are able to interact more closely and operate more demand-driven. This would allow, for instance, to shift off-label use of medicines to on-label use based on decisions made by authorities rather than industry (in the sense of repurposing or adding an additional indication). It would also allow payers to determine the required information upfront and tailor files towards patient-oriented outcomes to inform pricing and reimbursement decisions.

- **Future-proof legislation for access to EU markets**
  - The current system is tailored towards pharmaceutical products for larger groups of people. This caused a focus on the market authorisation as a final result. In a changing world, the market authorisation on a classical basis is less feasible for personalised medicines or products targeting small patient groups.
  - Therefore, alternative routes of access should be identified and supported as well as possibilities in accounting for new technologies (like Big Data, AI, advanced therapies etc.) to keep pace with the rapid advances in science and technology.

- **Regulatory optimisation to ensure real access to needed medicines**
  - The current pharmaceutical framework contains several procedures and requirements that do not contribute to patient health. Optimizing legislation with the aim to reduce unnecessary administrative and regulatory burden will have a positive effect on the availability and innovation of medicines as well as on pricing and reimbursement.
  - In addition to strengthening safety and security, effectiveness and quality of medicines and their production, including environmental protection, legislation should support improving both availability and affordability of medicinal products. The latter are key dimensions of access.
  - The Commission together with the Member States should consider ways to enable and stimulate, from the beginning, a structural dialogue between regulatory authorities, HTA bodies and payers, managing the complementary character of their different responsibilities and facilitating the access to new health technologies. Such an early three-party dialogue could then become the standard approach towards processes leading up to (applications for) marketing authorisations.

- **Legislation needs to allow for improved collaboration**
  - Cross-country collaboration has proven increasingly important in order to achieve long-term access to innovative medicines and an innovative, yet competitive climate and optimal care for patients. Legislation should focus on enabling and optimising opportunities for collaboration of public entities across borders and from a holistic view along the pharmaceutical value chain and at an early stage, as a tool to operationalise solidarity across countries and strengthen the balance between the public and private sectors.

- **Transparency**
  - Transparency is not an endpoint in itself but a way to ensure good practice and well-informed decision-making. Transparency as one of the principles of good governance is currently not addressed with the necessary attention in the revision process. The pharmaceutical system is opaque. The lack of transparency around the costs of research and development (R&D),data and results (e.g. clinical data and environmental risks data), public investment, products in the pipeline and both actual cost of medicines as well as the actual price in each Member State impairs the ability of Member States to make fully informed decisions when purchasing medicines or negotiating the prices for their populations. The principle of transparency in processes and results should be integrated into pharmaceutical legislation as far as possible, addressing both stakeholder's as well as public authorities' responsibilities.

Substantiation of the responses of the Netherlands to the questionnaire in relation to the revision of the EU basic pharmaceutical acts

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Q1 In your opinion, are there any other issues that should be addressed in this revision?

1. Integrated approach:

The review of EU pharmaceutical legislation should not only look at the individual legislative acts, but integrally at all pieces of legislation to identify overlaps, redundancies and inefficiencies. In addition, the usefulness and necessity of one integral piece of legislation instead of several separate frameworks should be considered. An integrated approach should also look at gaps, inconsistencies, coherences, redundancies and overlaps with other frameworks impacting developments in the area of pharmaceuticals and pharmaceutical use, notably the Clinical Trial Regulation, the GMO-legislation, legislation on substances of human origin and frameworks for intellectual property, digitalisation etc.

2. Regulatory optimisation:

Considerable time is spent by both competent authorities and industry on procedures and activities with no or limited impact on public health. Reducing the administrative and regulatory burden for all stakeholders involved results in reduced costs, allows freeing up capacity and creates a more attractive market environment for pharmaceuticals. This has a positive impact on the availability and innovation of medicines as well as pricing and reimbursement, and allows for prioritising activities and products with added-value to patients.

In addition to strengthening safety and security, effectiveness and quality of medicines and their production, including environmental protection, legislation should support improving both availability and affordability of medicinal products. The latter are key dimensions of access.

The Commission together with the Member States should consider ways to enable and stimulate, from the beginning, a structural dialogue between regulatory authorities, HTA bodies and payers, managing the complementary character of their different responsibilities and facilitating the access to new health technologies. Such an early three-party dialogue could then become the standard approach towards processes leading up to (applications for) marketing authorisations.

3. Future-proofing of the legal frameworks:

a. <u>New routes of admission to the market and accounting for new technologies</u>

In general, the regulatory pharmaceutical framework lacks the flexibility to adequately respond to digital, scientific and technological advances. As a result, it falls short from a public health perspective.

More specifically, it is mainly focused on medicines for large groups of patients, resulting in a focus on the marketing authorisation as the end result. However, the marketing authorisation is not a viable outcome for all products, especially for those for very small patient groups and for personalised medicines. Nevertheless, these products are the future. In order to get these products on the market, other routes of market admission must be considered.

In addition, legislative possibilities should be explored accounting for new technologies, such as Big Data, Artificial Intelligence, 3D printing and advanced therapies, to keep pace with the rapid advances in science and technology.

b. <u>Revision of the ATMP framework</u>

It is insufficient to only revise the basic pharmaceutical acts to achieve a truly future-proof framework. The regulation for advanced therapy medicinal products (ATMPs) should be revised integrally as it raises several challenges and has shortcomings. Production processes are sometimes (partly) decentralised (e.g. in hospitals as opposed to central manufacturing in one or a few sites globally), some therapies can be tailored to specific patients, but the procedures for centrally-approved marketing authorisation and hospital exemption might not be optimally adapted to these therapies. These circumstances raise several questions: how do we ensure an assessment of the quality, safety, efficacy and effectiveness of these therapies, while also granting sufficient room to encourage new scientific developments and possibilities? What should be assessed, the customized therapy or the associated technique or process steps? These are issues that require further examination at the EU level. In the short term, we would recommend a dialogue on and assessment of these questions. In the long term, a review of the current ATMP legal framework and, where

necessary, changes to this framework should be introduced to facilitate and stimulate the uptake of these innovations.

4. From an applicant-driven to a system that is also regulator- and payer-driven:

Currently, pharmaceutical industry determines what data is submitted and when. However, there is a need for a more patient-oriented approach, where regulators and payers are able to interact more closely and operate more demand-driven. A system that is also authority-driven better serves the patient, because, for example, it allows converting off-label use to on-label based on decisions made by authorities rather than industry (in the sense of repurposing or adding an additional indication), thereby, among others, reducing safety risks. Regulatory procedures to approve a new therapeutic indication entail a high administrative and regulatory burden and significant costs, which may deter companies to submit such an application. In a system that is also regulator-driven, however, competent authorities can determine that an off-label indication can be on-label based on experience gained, so that an applicant only has to update the product information accordingly via a simple administrative procedure (without the need to submit all study data). A recent example of how this could work is the Art. 5(3) opinion on dexamethasone for Covid-19. In addition, a system that is also authority-driven would allow payers to determine the required information upfront and tailor files towards patient-oriented outcomes to inform pricing and reimbursement decisions.

5. Differentiated incentive scheme:

On the premise that incentives only reward exceptional products, there should be a more differentiated incentive scheme.

6. Legislation needs to allow for improved collaboration

Cross-country collaboration has proven increasingly important in order to achieve long-term access to innovative medicines and an innovative, yet competitive climate and optimal care for patients. Legislation should focus on enabling and optimising opportunities for collaboration of public entities across borders and from a holistic view along the pharmaceutical value chain and at an early stage, as a tool to operationalise solidarity across countries and strengthen the balance between the public and private sectors.

7. Transparency

Transparency is not an endpoint in itself but a way to ensure good practice and well-informed decision-making. Transparency as one of the principles of good governance is currently not addressed with the necessary attention in the revision process. The pharmaceutical system is opaque. The lack of transparency around the costs of research and development (R&D), clinical trial data and results (e.g. , clinical data and environmental risk data), public investment, products in the pipeline and both actual cost of medicines as well as the actual price in each Member State impairs the ability of Member States to make fully informed decisions when purchasing medicines or negotiating the prices for their populations. The principle of transparency in processes and results should be integrated into pharmaceutical legislation as far as possible, addressing both stakeholder's as well as public authorities' responsibilities.

Reference is also made to the Joint Statement of NIHDI (Belgium) and the Netherlands, members of the Beneluxa initiative (Annex I).

Q2 How has the legislation performed in terms of the following elements?

In general: As already stated under Q1, the current pharmaceutical legal framework is mainly focused on medicines for large groups of people, resulting in a focus on the marketing authorisation as the end result. However, this is not a viable outcome for all types of products and, hence, other routes of market admission should be considered.

Q2.3: Over the last couple of decades, the cost and time to market for new therapies have soared. While a fair number of causes need to be sought outside the regulatory framework, it remains necessary to look critically at requirements and processes stemming from the legal framework. For example, during the current crisis it appeared that faster outcomes are possible. For example, for the Covid-19 vaccines it was quickly agreed what clinical research was needed, and Covid-19 vaccines and medicines have been developed without the need for additional incentives. Also, the current regulatory system allowed for introducing additional regulatory flexibility for Covid-19 products. Clearly formulated and frictionless coherence between different parts of the legislation

should support the practice of drug development.

Q2.4: Several routes of early access schemes are available (conditional marketing authorisation, PRIME), which are important tools to speed up availability of important, innovative therapies to patients. However, the regular 210-day marketing authorisation procedure could benefit from a re-evaluation in terms of, among others, efficiency and redundancy.

Q2.6: The revision should allow for regulatory innovation to keep marketing authorisation requirements up-to-date. Among other things, developments in the fields of innovation of production, diagnostics, imaging, wearables organoids, data management and the avoidance of use of laboratory animals are important. In this regard, horizon scanning and looking for those innovations with the potential to transform healthcare and how it is provided should be helpful. Further, as stated already under Q1, the ATMP legislation should be integrally revised to achieve a truly future-proof pharmaceutical framework.

Q2.7: The system functions well in regards ensuring that products that enter the market meet the required high quality, safety and efficacy standards. In the post-marketing situation, however, the system should require more from companies with regard to keeping the medicine dossier up-to-date with regard to effectiveness.

Q2.8 and Q2.9: The system offers too many opportunities to 'game the system' at the expense of affordability and availability, for example in the case of repurposing of older/established medicines, and legitimises competition behaviour that would be unlawful in non-pharmaceutical markets. In the case of orphan medicines, the system has performed very poorly.

Q2.11: Shortages have been on the rise in Europe. Although supply issues are not necessarily a direct result of the current legislation, legislation could contribute to strengthening the security of supply.

Q2.12: The existing legislation is entirely devoted to patients' health through safety and efficacy. It ensures that high quality pharmaceutical products accompanied by the right information reach the right patient in the right way. However, environmental-friendly production is currently not within the scope of this legislation as it has no bearing on pharmaceutical quality nor on the delivery of pharmaceutical care. Further reference is made to Q12-13.

Q2.13: As also stated under Q1, regulatory optimisation could contribute to increasing the availability of medicines by reducing administrative and regulatory burden and, thereby, time and costs. This could decrease the bar for submitting requests for a marketing authorisation and stimulate that (older) products with a small profit margin are kept on the market. Regulatory optimisation would also include considering a single overarching piece of legislation that encompasses all types of products.

Q2.14: Incentives are not specific enough to steer towards innovations necessary for improving public health. This would require there to be mandatory elements that tie the research and development (R&D) to the EU. Think of requirements to perform clinical research in the EU to be eligible for incentives. Or to develop incentives that stimulate R&D into unmet needs specific to the EU.

Other: Currently, pharmaceutical legislation, including the Falsified Medicines Directive, does not allow for the re-dispensing of unused, already dispensed medicines. This has undesirable environmental and, especially in case of expensive medicines, economic effects. In light of Europe's sustainability goals, and in particular the EU Green Deal, and in order to reduce ever increasing healthcare costs, possibilities for re-dispensing unused (expensive) medicines should be looked at whilst ensuring product quality and authenticity and, hence, patient safety. This would require amendment of existing legislation, including the Falsified Medicines Directive.

Q3 How important are the following elements for defining 'unmet medical needs'?

Q3.1: Seriousness of disease is a relevant criterion to look at. However, 'seriousness of disease' should be clearly defined.

Q3.2: This criterion should not be limited to authorised treatments. Instead, it must be checked whether off-label use according to accepted guidelines or pharmacy preparations cannot already meet the need. Also, the definition of 'satisfactory' needs attention.

Q3.3: The definition of 'major' needs to be specified. Also, curative therapies versus medicines that control symptoms could be considered as relevant criterion.

Q3.4: Distinction is needed between lack of access (there is a medicine but it is not marketed everywhere) and lack of availability (there is no medicine) as these issues need different solutions. In addition, as stated under Q3.2, if off-label therapies and/or pharmacy preparations are available, there is no real unmet medical need (UMN).

Q3.5: When defining an UMN, the aspect of time should be considered as unmet needs change over time, e.g. because more treatments become available for a particular condition. In addition, even in case one or more medicinal products are available for a particular indication, it may not be suitable for all patients (including all age groups for children) they were intended to serve, for instance (big) tablets for patients with difficulty swallowing. This should be taken into considering when defining UMN. In addition, legislation should not hinder the role of pharmacies in on a small scale adjusting the dose/formulation/route of administration of existing medicines to suit the needs of an individual patient.

Q4 What do you think of the following measures to support innovation, including for 'unmet medical needs'?

Q4.1: The current data and market protection periods are too unfocused, one-dimensional and vulnerable to gaming the system.

Q4.2 - 3: Linking the duration of the data and market protection periods to the purpose of the medicine is supported. However, an extended period of monopoly as compared to the current situation can only be justified if needed to ensure return of investment and when justified from a public health need point of view. A reduction of the current data and market protection period for certain products needs to be carefully assessed first, weighing the potential benefits (earlier access for generics/biosimilars to the market) against potential undesirable effects (e.g. a negative impact on innovation).

Q4.4: The Netherlands is interested in exploring potential novel incentives, however, we are not convinced the examples provided (transferable vouchers and transferable priority reviews) are suitable tools. If introducing new types of incentives, we should be wary of potential unintended side-effects, and any novel incentive that is considered must stimulate research and development of medicines intended for the greatest unmet medical needs, without a negative impact on accessibility and affordability. It would be very difficult, if not impossible, to determine the effects of transferable exclusivity vouchers or transferable priority reviews on the availability and affordability of medicines.

Q4.7: Insight into the cost elements is necessary, i.e. in order to allow payers to ensure acceptable pricing and reimbursement decisions. This will warrant actual access to medicines that address high unmet medical needs.

Q4.8: To address the issue of pull incentives for antimicrobial resistance (AMR), financial incentives are required, not regulatory incentives. Pull incentives should be direct financial incentives, such as market entry rewards. Extending for instance market exclusivity will not be enough, as the sale volumes will remain too small to incentivize the required innovation.

Q5 Should there be specific regulatory incentives for the development of new antimicrobials while taking into account the need for more prudent use and if so what should they be?

New business models are required to stimulate development of antimicrobials that will only be used if all else fails (reserve products). This also applies to already authorised products that are not or no longer in use, as in the (near) future a situation may occur that requires the use of these

antimicrobials.

As stated under Q4, to address the issue of pull incentives for antimicrobials, financial instead of regulatory incentives are required. These incentives should be direct financial incentives, such as market entry rewards or something similar. Extending for instance market exclusivity will not be enough, as the sale volumes will remain too small to incentivize the required innovation. Further, reducing the regulatory and administrative burden will contribute to innovation and the staying on the market of older products. As regards marketing authorisation, antimicrobials may qualify for faster approval schemes and extended protection periods.

Nevertheless, while investment in and appropriate incentives for new antibiotics are needed, if these are not used prudently, then antimicrobial resistance is likely to persist. Priority should be given to reducing unnecessary antibiotic use by changing the regulatory framework in such a way that it promotes personalised and evidence-based treatment (use of diagnostic tests) where and when possible. In addition, all antibiotics should be classified as prescription-only across the EU.

Q6 How would you assess the following measures to create an adapted, agile and predictable regulatory framework for novel products?

Q6.1: The intended revision should use the opportunity to resolve issues regarding relevance, redundancy, incitement of/vulnerability to misuse or unintended consequences. Any gaps, overlaps and coherences between the different legislative instruments impacting pharmaceutical developments and use, for example the Clinical Trial Legislation, should be taken into account.

Q6.2 and Q6.4: One important challenge is to clarify the interaction and the border between the regulatory frameworks for pharmaceuticals, medical devices and SoHO products (substances of human origin). Therefore, we support the proposal to create a central mechanism in close collaboration with the other concerned authorities to provide classification advice[1] and to create adaptive regulatory frameworks in coherence with other legal frameworks. The proposal to create an adaptive regulatory framework in coherence with other legal frameworks like SoHO suggests more harmonisation between the frameworks. However, we do miss a joint approach with the SoHO authorities directed towards clarification of the criteria in place determining when a SoHO should be classified as an AMTP or not. The criteria "severe manipulation" and "non-homologous usage" are multi-interpretable and, therefore, do not contribute to a harmonised approach within the EU and cause national classification difficulties. Notably, the regulatory SoHO framework is also under revision, through which structures are being developed to better deal with innovation and effectiveness of treatments. We strongly advocate to grasp this opportunity of the parallel revision of both the SoHO and pharmaceutical legal framework to initiate a joint approach between the pharma and SoHO authorities. This joint approach should focus on investigating how criteria can be established resulting in well-suited legislation for borderline medical products that eventually leads to the most optimal availability of treatments to patients.

This joint approach should also include the relevant authorities for medical devices, since the same issue applies for the border between the regulatory frameworks for pharmaceuticals and medical devices; there are products with a comparable mechanism of action that are on the market as a pharmaceutical product and as a medical device.

Q6.3: Sandboxes must be clearly defined with all stakeholders involved, including patients, and attention is needed to how these should be governed and who is responsible.

Q6.5: If such an EU-wide process is introduced, the division of competences should be respected, while information exchange between authorities is facilitated. Also, a proper system of horizon scanning should be used, and the EMA and HTA evaluation process should be aligned both in regards required data and timing (start of the evaluation).

Q7. Do you think that certain definitions and the scope of the legislation need to be updated to reflect scientific and technological developments in the sector (e.g.

[1] For reference, in the Netherlands a similar mechanism already exists where experts from the Medicines Evaluation Board (CBG/MEB), Health and Youth Care Inspectorate (IGJ), Food and Consumer Product Safety Authority (NVWA) and Central Committee on Research Involving Human Subjects (CCMO) advise on the status of a product in case it is not immediately clear whether it concerns a pharmaceutical, medical device or food supplement and, hence, which legislative framework applies.

personalised medicines, bedside manufacturing, artificial intelligence) and if so what would you propose to change?

Without being able to be specific for the time being, it is advisable to check during the intended revision whether the terminology used is still appropriate. Redefinition should be such that it is fit to tailor to future innovations for as long as possible.

Q8 How would you assess the following measures to improve patient access to medicines across the EU?

Q8.3, Q8.5 and Q8.6: EU-broad comprehensive standardised market introduction should in principle be the normal standard; incentives should be restricted to promote special medicinal products. However, it should be investigated whether a requirement of EU-wide marketing within a certain period (Q8.5) is achievable for all types of companies and products (i.e. SNEs or innovative products manufactured in a single production site).

Q8.4 and Q.8.6: These options need definition/standardisation of acceptable market introduction. Early introduction of generics in case the innovator is not available should be further investigated as an option to improve patient access, whilst carefully considering potential negative impacts on innovation.

Q8.7 - 8: More flexibility in regards the requirements for the packaging and product information could contribute to present the most up-to-date information to patients, to reducing shortages and to improve the availability of medicines in small(er) markets. However, there must be sufficient guarantees that the necessary information remains accessible to people with limited digital skills without increasing the administrative burden in the pharmaceutical chain.

Q8.9: Mandatory data acquisition for non-marketing authorisation treatments, including hospital exemptions, (ATMP) to enable a transparent process in the EU could be considered. More specifically, it must be clear which treatments are available where and under what conditions, so as to enable patient access and to potentially harmonise data to enable a normal regulatory process.

Q9 In your view, to what extent would the following measures support access to affordable medicines?

As a general statement, measures focused purely on the affordability and pricing of medicines are to be considered with caution as a too narrow profit margin will lead to the withdrawal of products from the market. Hence, a combination of measures is needed focusing on not just affordability but also security of supply and sustainability.

Q9.2: This option is unclear. We support that generic companies can conduct research on a patent protected medicine with a view to apply for a marketing authorisation, but we do not support the actual market introduction of a generic before the patent has expired.

Q9.3: Although we are not generally against incentives for generics and biosimilars, the option as proposed here is not supported. First, it opens the possibility to gaming by the originator, as they are in the position to develop a generic or biosimilar before all other parties, thereby blocking competition. In addition, this options results in fewer instead of more generics and biosimilars.

Q9.5: Joint procurement should not be used by default but could be a useful instrument in particular situations. Joint procurement could stimulate innovation and production of products where there is market failure such as antibiotics, and procurement between several Member States may for certain expensive products aid in achieving affordability and improved conditions. If used, however, it should be under the condition that participation and acceptance of the final outcomes of the process are strictly voluntary and do not limit national pricing and reimbursement competences. Also, joint procurement endangers market competition if a tender is given to a single company and, as a result, forces other companies to cease marketing their product. It should be realized that joint procurement may not contribute significantly to security of supply in general, since the aspects impacting security of supply are mainly risks in the supply chain, lack of substances and technologies, and lack of stimuli for innovation, production and sustainability.

Q10 What measures could stimulate the repurposing of off-patent medicines and provide additional uses of the medicine against new diseases and medical conditions? Please justify your answers.

Real-world data provides insight into the possibilities of daily used or off-label medicines.

In addition, as already stated under Q1, a shift from an applicant-driven system to a system that is also regulator-driven will serve the patient more adequately. It for example allows converting off-label use to on-label use by regulators, so that an applicant only has to update the product information accordingly via a simple administrative procedure (without the need to submit all study data).

Finally, the regulatory system should not allow the hijacking of medicinal products that are already used off-label and included in medical-professional treatment guidelines (i.e. giving long exclusivity periods for repurposed products for which limited budget and effort were required to gather the required data).

Q11 What is your view on the following measures to ensure security of supply of medicines in the EU?

Q11.2: Earlier notification of shortages can only help if it does not create too much uncertainty regarding a possible shortage and 'false positives'. This would make the administrative burden higher for both industry and government while not meeting the goal of addressing shortages. Earlier notification for market withdrawals could be useful as in some cases more time is needed to prepare when a product leaves the market completely. We support exploring whether a common EU-level format is possible.

Q11.4: Even though stocks do not seem to tackle the root causes of shortages, when a supply chain is vulnerable, stocks can help to temporarily mitigate the problem to lower the (direct) impact on patients. When it comes to a 'sufficient amount of stock', both how companies interpret this and the rules that different EU countries have vary greatly. We are therefore in favour of a quantification of 'sufficient amount of stock'.

Q11.5 – 6: Security of supply, ensuring sufficient stock, and signalling and monitoring (potential) shortages are firstly the responsibilities of the marketing authorisation holder (MAH). More dialogue is needed to determine in which cases a more elaborate central monitoring system could be helpful, without shifting these responsibilities.

Q11.7: Diversification of supply chains is important, but the possible impact on costs and, therefore, on the availability of products should also be investigated.

Q11.8: More transparency about the design of their supply chain, choices that are made and the rationale behind them could contribute to insights into shortages. However, it is important to first determine what the regulator will and can do with this information in order to avoid unnecessary administrative burden.

Q11.9: Attention is needed to the design of the enforcement of penalties. In addition, consideration should be given that in certain situation penalties might be counter-productive. We do however support exploring whether a harmonised penalty system is possible as the differences between countries are now large.

Q11.11: First of all, it is very important that any potential measures that are taken are as evidence-based as possible and can truly tackle the root causes of shortages. In this regard, we should also evaluate whether there is a one-size-fits-all solution for all medicines and shortages or whether a more customized approach is needed for different product groups (e.g. critical medicines).

Besides shortages resulting from manufacturing or quality issues, in some cases certain choices by the MAH but also distributors when allocating stocks are made based on commercial reasons, which can lead to shortages in specific countries. More insight is needed in the incentives that play a role in this process and how we can ensure that stocks are allocated in a matter that best serves the patient.

Furthermore, the new Dutch government has confirmed the political importance of enhancing the EU's open strategic autonomy. The Netherlands is committed to decrease EU's dependencies and vulnerabilities related to the production and supply chains of pharmaceuticals and their needed starting materials and technologies.

Q12 What is your opinion of the following measures to ensure manufacturing and distribution of high quality products?

Q12.4: Within the pharmaceutical domain many quality systems exist. However, the concept of high-quality products is not related to environmental parameters in manufacturing and distribution. For instance, Good Manufacturing Practice (GMP) is entirely devoted to the reproducible production of pharmaceutical products as to ensure technical quality, therapeutic efficacy and patient safety. Environmental parameters have no bearing on quality, efficacy or patient safety and, therefore, do not fit the purpose of GMP. And healthcare inspectorates have background nor mandate in environmental matters. GMP does mention the proper handling of waste, but this is not specified. Perhaps a separate quality system of Good Environmental Practice (GEP) could be introduced for the pharmaceutical realm, whilst accounting for a potential overlap with existing legislation on hazardous substances.

Consideration should be given on how environmental risks of not just authorised but also unauthorised medicines can be addressed as they may be used industrially without a valid marketing authorisation (e.g. obsolete antibiotics in cell cultures). Consequently, also the regulatory status of active pharmaceutical ingredients that are traded, distributed or used as chemicals should be clarified in relation to environmental issues.

Q12.7: The focus should not only be on rules and requirements laid down in legislation. Increased mutual involvement and cooperation between licensing and inspecting authorities could help to (more) automatically incorporate and increase in legislation the flexibility needed for new techniques and new ways of manufacturing. Such cooperation could take place in both the pre- and post-approval phase of a regulatory procedure. To involve companies in such a route and in order to facilitate innovation, it may be considered to develop a kind of extended scientific/regulatory advice procedure for manufacturing and distribution approaches that are currently not covered by the regulation.

Q13 How would you assess the following measures to ensure that the environmental challenges emerging from human medicines are addressed?

Q13.1: As a general statement, any measures to be developed and implemented to prevent or mitigate environmental risks should not jeopardise the availability, accessibility and applicability of medicines. Nevertheless, action is required to reduce the impact of the production, use and disposal of medicines on the environment as pollution caused by pharmaceuticals bears risks to not just the environment but also human health, especially in relation to the growing problem of antimicrobial resistance.

Q13.2: The legislative option of including an environmental risk assessment (ERA) in the benefit/risk analysis cannot be supported, because, as stated before, any actions to mitigate environmental risks should not affect the availability, accessibility and applicability of medicines. Also, environmental risk(s) will most likely always be outweighed by patient benefit, leading to a 'window dressing exercise' that works counterproductively, whereby the technical part of the risk assessment might become eroded or undermined to prevent the active ingredient from meeting the threshold of high risk- or hazard-criteria. Nonetheless, the current system should be changed as the ERA outcome bears no consequences as regards responsibilities and follow-up actions. Legally binding mechanisms should be considered to enforce both a timely and complete ERA dossier at the time of submission as well as risk mitigation measures in case of a (potential) risk. In addition, when monitoring shows that environmental risk limits (Water Framework Directive Environmental Quality Standards or PNECs from the authorisation framework) are exceeded, this should feed back into a mandatory regular review of the ERA.

Q13.3: The reason for differing assessment results among various Member States (leading to diverse conclusions for similar products) is the varying level of expertise and capacity. This gap can be addressed by offering additional training and educational support and installing a formal ERA

working party at the EMA.

In addition, instead of having individual ERAs for each marketing authorisation application, a central substance-based assessment similar to what is currently done for the Active Substance Master File (ASMF) should be considered. The results of these tests could then be used for the environmental risk assessment of individual products, given that each has their own use and corresponding exposure profile. A substance-based system would prevent variability in dossiers (and their conclusions) for different products containing the same active substance as well as the repetition of (animal) studies for eco-toxicological purposes.

Q13.4: It should be ensured that data on environmental risks are easily accessible and understandable to all interested parties, i.e. health care professionals (HCP) and the general public, but also the water sector. The purpose is to promote the rational and prudent use of medicines (HCP, general public) and to enable a thorough understanding of the environmental risk of substances and allow for adequate monitoring and proper measures (water sector). However, only if information is user-friendly, well-balanced and tailored to target audiences' needs the relevant party can respond adequately.

More transparency on environmental data could also support informed decision-making in regards 'responsible procurement' of products. It should be investigated how legislation could promote such transparency.

Q13.5: Pharmaceutical industry (EFPIA, AESGP, EGA) have proposed in their eco-pharmaco-stewardship initiative - pillar 3 'Extended Environmental Risk Assessment' - the development of a system for ERA-data and cost sharing between originator and generic companies, followed by a regular re-evaluation. This industry proposal could be fully endorsed, but in case of endorsement it should be made mandatory.

Q13.6: The pharmaceutical legislation should be linked to legislation on water, chemicals and the environment as well as to the EU Green Deal's chemicals strategy for sustainability to enable and promote communication between the different sectors. Further, the development of personalised medicine and the improvement of diagnostic and delivery methods to reduce the use of pharmaceuticals should also be stimulated.

As stated under Q2, pharmaceutical legislation, including the Falsified Medicines Directive, does not allow for the re-dispensing of unused, already dispensed medicines. This has undesirable environmental and, especially in case of expensive medicines, economic effects. Hence, possibilities for re-dispensing unused (expensive) medicines should be considered, whilst ensuring product quality and authenticity.

Q14 Is there anything else you would like to add that has not been covered in this consultation?

We would like to reiterate once more that the review of the pharmaceutical legislation should:

1. take an integrated approach looking at gaps, overlaps, redundancies, coherences and contradictions between all pieces of pharmaceutical legislation and between pharmaceutical legislation and other frameworks, i.e. the Clinical Trial Regulation, the GMO legislation and the SoHO legislation;
2. lead to a more lean, simplified framework with reduced regulatory and administrative burden for all stakeholders involved;
3. consider new routes of admission to the market and have attention for AMTPs and new technologies in order to create a future-proof regulatory framework;
4. allow for a system that is not just applicant-driven but also authority-driven;
5. consider a differentiated incentive scheme rewarding exceptional products;
6. allow for improved cross-country collaboration between public entities at an early stage;
7. pay attention to transparency as one of the principles of good governance.