The Netherlands: Key messages in response to the public consultation on Pharmaceuticals – safe and affordable medicines (new EU Pharmaceutical Strategy)

15 September 2020

We welcome the opportunity to respond to the open consultation of the European Commission on the Pharmaceutical Strategy.

Access to affordable medicines and a **healthy, competitive EU market** are crucial for the health of the European people and for the security and autonomy of the European Union. Medicinal products are not only essential to the wellbeing of citizens, but also of strategic importance to the EU's industrial landscape. The European pharmaceutical industry plays a valuable role in the research and development of innovative treatments and in the production of key enabling technologies. Ensuring the **supply of high quality, safe, efficacious and affordable medicines** in the single market is urgent and decisive to the future of the European Union.

Stepping-stones for the future pharmaceutical strategy:

- Creating a holistic and concrete strategy in constant cooperation with Member States.
- Basing the strategy on evidence and thorough analysis and sharing that with Member States.
- Designing a strategy, centered on patients, health workers and health systems and responding to their real needs.
- Respecting the division of competencies and powers of Member States and the EU Commission.

FOSTERING PHARMACEUTICAL INNOVATION that meets public and patients- needs by:

- Defining the term 'Unmet Medical Needs' in close dialogue with Member States.
- Adapting the EU pharmaceutical legislative framework to respond to technology advances in medicinal products, their production and post-authorisation lifecycle management
- Initiating a dialogue with Member States on 'Advanced Therapy Medicinal Products' and reviewing their European legal framework.
- Reviewing the variation framework, to minimise administrative and regulatory burden and simplify procedures

STRIVING FOR EQUAL ACCESS by assuring SUPPLY, AVAILABILITY, AFFORDABILITY by:

- Gathering data and analyzing dependencies and weaknesses to map the vulnerability of the pharmaceutical chains.
- Addressing pharmaceutical chain vulnerability by diversifying sourcing and suppliers, building larger stocks at European level and incentivizing relocation of production locations to the European Union.
- Dealing with circumstances leading to market withdrawals by simplifying of the procedure for variations and introducing multi-language packaging information and e-leaflets to ease redistribution of medicines across the EU.
- Discussing the need and the scope of medicines listings.
- Promoting Member States cooperation to tackle shortages collectively and achieve equality of access, affordability and future-proof availability of medicines
- Paving the way to technical collaboration in HTA through joint alliances.
- Facilitating debates on transparency of costs of research and development

- Addressing selective market introduction by requiring Market Authorization Holders to market their product in all Member States once its centralized marketing authorization has been granted.

ENCOURAGING SUSTAINABLE PRODUCTION, USE AND DISPOSAL by:

- Tackling residues of pharmaceutical products and Antimicrobial Resistance

TAKING STOCK ON LESSONS LEARNT from the coronavirus (COVID-19) pandemic:

- At national level, the need to monitor closely the supply and the market and discuss solutions with pharmaceutical chain stakeholders.
- At European level, the importance of upholding European solidarity and collaboration by promoting positive actions, exchange of information and good practices, foresight of upcoming initiatives, efficient consultation and coordination structures.

Stepping-stones for the future pharmaceutical strategy

Creating a strategy that is holistic, but concrete - While we welcome an all-inclusive strategy, further clarification, discussion and translation of the objectives into concrete and operational actions are needed.

Basing the strategy on evidence and thorough analysis and sharing that with Member States- The development of the pharmaceutical strategy and its ensuing measures are to be based on evidence and analysis. Therefore, studies on which the European Commission will build the pharmaceutical strategy must be shared in a timely manner, in order to stimulate debate and exchange of views between the Member States and the Commission. This would include inter alia granting access to any studies, their terms of reference, results, related reports as well as the Commission's analysis thereof.

Designing a common strategy, centered around users and responding to real needs - The pharmaceutical strategy should result from a collaboration between the European Commission and all Member States. This is essential to ensure that the content of the pharmaceutical strategy meets the needs of its target groups, i.e. the Member States at a macro-level, cascading ultimately into their health systems, their health professionals, their patients and their citizens at grass-root level. It should therefore be user-centric. This requires active dialogue with the various stakeholders and joint preparation of its content.

Jointly-developed working plan - The publication of the Commission strategy should be followed up by a concrete working plan on pharmaceutical policy (2020-2025) in close cooperation between the Member States and the European Commission. This would involve defining a joint programme of objectives and concrete short-term activities, engaging the Member States in the planning and development process, defining coordination roles, and establishing clear and transparent governance and procedures. All this while ensuring proactive exchange of information between the Member States and the Commission.

Encouraging coherence across ongoing and upcoming EU policies - The European Commission is currently developing and/or discussing several initiatives that have great implications for the future European pharmaceutical strategy. We propose linking the various components of the upcoming Pharmaceutical Strategy with the new Industrial Strategy for Europe, the European Green Deal, the IP Action Plan, the research and development policy (namely the pharmaceutical R&D within Horizon Europe), the Strategic Approach to Pharmaceuticals in the Environment, the Chemicals Strategy, as well as the EU recovery plan and its EU4Health programme, to duly align overarching objectives and strategic measures.

Aligning the strategy to the division of competencies and powers between the EU and Member States and respecting the distinct roles of the Commission and the Member States.

In terms of content, we note below several issues that we consider fundamental to the pharmaceutical strategy.

FOSTERING PHARMACEUTICAL INNOVATION THAT MEETS PUBLIC AND PATIENTS' NEEDS

Defining Unmet Medical Needs in close dialogue with Member States

To support innovative R&D, the EU legislation should become responsive to scientific and technology advancements. Support through funding of public-private partnerships would help align innovation towards public priorities. Yet to be successful, such an initiative would need to be collective. The European Commission could play a role here, by stimulating a debate with Member States on the definition of 'unmet medical need' to identify those priorities, i.e. the target conditions, technologies or patient groups to be addressed by new therapies. Specific European funding can then be directed towards financing research and development for those established unmet medical needs.

We agree that it is important to establish a definition for 'unmet medical need' within the European Union. This should linked to an established timeline, to be agreed beforehand. If a given unmet need is defined for indication A and over 5 or 10 years (the established period) several products are approved to treat that condition, there should be a mechanism or process available through which the initial decision can be revoked, so that condition A would no longer qualify as an unmet medical need. We would also advocate to stimulate research in targeted areas at EU level, as it allows allocation of public investment and fine-tuning of key priorities. Depending on the target identified – by condition, by technology or by patient group – a funding instrument would need to be defined.

Adapting the legislative framework to respond to technology advances

The legislative framework for lifecycle management is too burdensome, both from a regulatory and administrative perspective, lacking the flexibility to respond to digital, scientific and technological advances. For instance, the regulatory framework is not well-suited to increasingly complex products nor to the implementation of continuous manufacturing or performance-based approaches to manufacturing and control. The current opportunities for regulatory flexibility towards CMC provided by the framework (e.g. design space, PACMPs) are underused or have limited usability due to lack of harmonisation across regions and a vigilant approach from regulators. Consequently, there is a delay in implementation of innovations in manufacturing and control processes of products and changes in such processes are not always promptly addressed or approved by regulators and across all regions.

New technologies, such as 3D printing of pharmaceutical products seem promising, as they are likely to allow tailoring of therapy to meet patients' needs, which is of interest for elderly and children, and could contribute to better adherence to therapy. However, it is an example of a regulatory "grey" zone, which current regulation does not clearly cover.

Promoting dialogue on Advanced Therapy Medicinal Products and reviewing their legal framework

Technology moves at a fast pace. It is challenging to get technological advances approved, as the process of submission and marketing approval is time-consuming. The central marketing authorization leads to a standardization in safety and efficacy, but also introduces some caveats, among which time-lagging and rigidity. For some therapies (such as Advanced Therapy Medicinal Products) marketing authorization holders have become more reliant on decentralized procedures and technologies, which in turn pose different challenges.

Over the past years, the first Advanced Therapy Medicinal Products (ATMP's) have received marketing authorization or approval under the Hospital Exemption. Many developments and

innovations within ATMP's benefit patients. The definition of ATMP also encompasses various types of therapies with differing characteristics. Some are like classic medicinal products as we know them, while others differ fundamentally as to standardization (for instance, autologous products whereby end-products vary) or even resembling medical devices (such as decentralized 'kits' for point-of-care).

The current legal framework for Advanced Therapy Medicinal Products (ATMP) raises several challenges and has shortcomings. Production processes are sometimes decentralized (as opposed to central manufacturing in one or few sites globally), some therapies can be tailored to specific patients, but the procedures for centrally-approved marketing authorization and hospital exemption do not seem to be sufficiently flexible.

These circumstances raise several questions: how do we ensure an assessment of the efficacy, safety and effectiveness for 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 which require further scrutiny at EU level. In the short term, we would recommend a dialogue and assessment of these questions. In the long term, a review of the current legal framework and where necessary, changes should be introduced to facilitate and stimulate the uptake of these innovations.

Pediatrics

The Pediatric Regulation establishes that research in children is mandatory for every medicinal product for which a marketing authorisation will be requested. Since 2007 pediatric development joins with the development for a medicinal product for the adult population. Therefore, there is no longer a need to grant an incentive for a mandatory action.

The Pediatric Regulation also provided an incentive to initiate pediatric research with existing medicinal products, for which a 6 month SPC extension could be granted. However, this catch-up effort is now finalised and since 2007 pediatric research is mandatory along with development of a medicine for adults research.
The Pediatric Regulation does not stimulate the development of diseases which occur only in children. These developments should be stimulated through other systems.

Reviewing the variation framework, to minimise administrative and regulatory burden and simplify procedures

The current variation framework, which was adopted in 2008 and consists of both the Commission Regulation (EC) No 1234/2008 (hereinafter the 'Variation Regulation') and its guidelines on the categorisation of variations (hereinafter the 'Classification Guidelines'), falls short from a public health perspective.

The variation framework has brought some advantages as compared to the previous framework. It is descriptive in nature and, therefore, predictable. It also introduced the possibility of work sharing, the grouping of variations and the annual update, all of which allow, in principle, a more efficient submission of post-authorisation changes.

However, the current framework is burdensome and lacks flexibility to respond to digital, scientific and technological advances. Considerable time is spent by both competent authorities and industry on administrative procedures of changes with no or limited impact on public health, at detriment of changes with high-risks and of added value to patients.

The regulatory tools for grouping and work sharing are not used optimally and, in some cases, can contribute to greater administrative and regulatory burden. For instance, under the former Variation

Regulation, the optimisation of the finished product was submitted as a single Type II, whereas it requires nowadays a grouped variation where every single change is to be indicated as a distinct variation. Similarly, a single active substance (dossier) is often used for several finished products owned by different marketing authorisation holders, which under the current framework leads to several identical regulatory submissions when a change is applicable to that dossier.

Furthermore, the variation framework was created more than a decade ago when digital solutions for administrative and regulatory processes were considerably less developed and available.

In addition, for biologicals and herbals, the Classification Guidelines do not reflect the actual risks that could ensue from certain changes. At the time of the adoption of the variation framework, we knew less about this type of products and, hence, several changes that would be labelled as a Type I variation for small chemical entities, were classified as Type II for biologicals and herbals. We have gained considerable knowledge and experience about these products since then, which calls for a re-assessment of classifications, especially for well-established types of products.

Similarly, the variation framework does not stimulate or incentivise enhanced company knowledge of manufacturing and control processes and, more specifically, of inputs and critical quality attributes (outputs). Both the Variation Regulation (Recital 3 and Article 4.1) and its Guidelines provide that the various categories of variations are to be updated regularly in light of scientific and technical progress, and take into account developments regarding international harmonisation and the Article 5 recommendations. However, the last update took place seven years ago (August 2013). Finally, the variation framework should also reflect the adoption of the Veterinary Medicinal Products Regulation, which provides a system to introduce changes to the marketing authorisation, which is independent from the Variation framework.

Due to the above-mentioned factors, we consider that the variation framework is no longer fit-for-purpose. It should be revised to:

- foster digital, scientific and technological innovation and continuous improvement in medicinal products, their production and post-authorisation lifecycle management;
- prioritise activities and products with added value for patients;
- stimulate or incentivise enhanced process and product knowledge;
- improve product supply and availability.

STRIVING FOR EQUAL ACCESS BY SECURING SUPPLY, AVAILABILITY, AFFORDABILITY

Addressing pharmaceutical chain vulnerability by diversifying sourcing and suppliers, building stocks and incentivizing production relocation to the EU

The (global) pharmaceutical chain of production and supply is vulnerable due to several factors among which the reduced number of production locations globally and the concentration of production locations in certain countries. This concerns not only the production of finished products, but also raw materials and intermediate products. The reduced number of production locations cannot respond promptly and increase production when needed. Currently, fewer stocks of finished products are being kept due to 'just-in-time-delivery' principles, which also contributes to the vulnerability of the chain.

The crisis highlighted **existing vulnerabilities** in medicines' availability as well as **one-sided dependencies** in raw materials and product supply from a few third countries. We encourage a European response to medicines shortages, which can encompass a diversification of sourcing and suppliers, larger stocks and a greater stimulus for relocation of production locations. These measures would aim to increase the resilience of the pharmaceutical chain and enable an efficient

response to peaks in demand, whereby the EU could be leading in innovative, sustainable, efficient and cleaner production. We welcome the coordinating role of the EU Executive Steering group on shortages of medicines caused by major events that was chaired by the European Medicine Agency (EMA).

Our aim is to achieve a healthy investment climate and ecosystem within the EU, where we can foster innovation and decreased undesirable dependency and vulnerabilities in medicine supply and where public and private interests are well-balanced.

Gathering data and analyzing dependencies and weaknesses to map the vulnerability of the pharmaceutical chains

Medicines' shortages are a serious worldwide problem, with an increasing trend of shortages being reported annually. In the short term, we would recommend obtaining greater insight into the facts and figures behind the causes of medicines' shortages in Europe. Better knowledge of dependencies and vulnerabilities is needed, both from outside Europe and among Member States, also to establish effective solutions. The research being conducted by the European Commission is very relevant and results should be shared promptly. We also support continuous information exchange among Member States about chosen approaches and their results, as well as sharing of lessons learnt. The European cooperation on shortages established during the COVID-19 crisis should be further evaluated and discussed, to take stock on the experience gained and define a productive way forward. Based on the results thereof, a consistent, longstanding European approach needs to be drafted, which should include both short-term and long-term actions.

Tackling shortages collectively through European Cooperation

We highlight the need for additional solidarity and cooperation among EU Member States to tackle collectively medicines shortages. Actions should focus on elements where a European approach is necessary and more effective than national initiatives, such as: increasing the availability of stocks in Europe; changing labelling requirements to ease redistribution of medicines across the EU; decreasing the dependencies from third countries by stimulating the production in Europe; harmonizing at EU level the monitoring of national stocks.

Introducing multi-language packaging information and e-leaflets

The introduction of packaging information in various languages and the dissemination of electronic product information could facilitate the circulation of pharmaceutical products across European Member States.

Optimizing existing supply chains

Any changes to the supply chain are likely to have positive and negative implications to the sector and its stakeholders. Therefore, we would warrant a focus on optimizing the use of existing /upcoming suppliers (both in economic and quality factors).

The EU depends on few suppliers of finished products, raw materials and semi-finished products. Other suppliers are only partially able to respond promptly to existing/upcoming shortages. The right incentives would help diversify supply at short-term and later increase production capacity within the EU. A differentiated medicines' supply chain, with sufficient stocks, would increase supply resilience, needed to provide patients the medications they need.

Discussing need and scope of medicines listings

Before deciding on which type of EU action or initiative is needed to incentivize the production of active pharmaceutical ingredients, it is necessary to further discuss the notion of essential medicines and whether such a list is needed at the EU level, as well as the possible criteria for inclusion. At this stage it is unclear whether the European Commission aims to build an inventory of basic medicines to meet most of European needs (general), or rather develop specific listings for treatments of key conditions that, due to their relevance, are considered critically important to be produced locally. After clarification of the aspects mentioned above and if list of essential medicines at the EU level does become available, then aspects to explore could include: the creation of tax incentives to stimulate companies to establish or relocate API producing plants to the EU; postulating or establishing innovative, technological requirements to lead companies towards sustainable production.

Promoting Member States collaboration – to achieve equality of access, affordability and future-proof availability of medicines

Pricing and reimbursement of medicines is and has traditionally been a national competence. Given the large differentiation of health systems, member states highly value the ability to determine the price and conditions under which medicines are made available to their patients.

At the same time, this has created a significantly fragmented market. Pricing of drugs is primarily determined internationally, allowing companies to benefit from a divided market, information asymmetries and varying abilities to assess and appropriately set pricing of pharmaceuticals. As countries increasingly face the same dilemmas of affordability and availability of medicines, collaboration is essential.

The strategic goal of the European Commission should be to honour national competences on pricing and reimbursement, yet simultaneously to optimize decision- making by facilitating collaboration among Member States.

Paving the way to technical collaboration through joint alliances

The arising regional alliances, such as the Beneluxa Initiative, have shown that technical collaboration can help bridge inequalities between countries and support efforts to increase affordability and availability. Learning from each other by exchanging policy best practices, sharing information, horizon scanning exercises and performing joint Health Technology Assessments (HTA) are important forms of –voluntary- collaboration, all aiming to fight market opacity and unequal access to medicines in Europe.

The Netherlands believes that the European Commission has an important role in aiding and facilitating collaboration between countries. Most notably, enabling information exchange between regional collaborations, as well as among individual Member States is key to achieve a more balanced pharmaceutical market across the European Union.

One of the examples which Member States acknowledge as valuable, through a more structural –voluntary- collaboration is Health Technology Assessment. The European Commission can play an important facilitating role in future joint HTA procedures led by Member States. Lessons learnt from the Joint Action EUnetHTA should ultimately lead to harmonized HTA methodology and joint HTA assessments being conducted throughout Europe. By doing so, a level playing field in national reimbursement decisions will be created among Member States, which can then become the stepping stone for joint price negotiations. Therefore, the Netherlands strongly supports the goals of the current legislative proposal on HTA.

New and promising technology developments and therapies pose new dilemmas. Yet there is limited, operational, policy exchange on how to accommodate for such advancements while ensuring the sustainability of our health systems. Debates on transparency or on a comprehensive

approach to the use of willingness to pay in price setting would benefit from a well-thought-out platform for information exchange.

Another area of collaboration which countries have implement to support their reimbursement processes, is horizon scanning. The International Horizon Scanning Initiative (IHSI) aims to generate predictive information on new therapies that could pose a challenge for countries. The Initiative consists currently of nine –mostly- European countries, yet all EU Member States might benefit from the type of information that is shared. It could eventually become the core for a coordinated approach to ensure all European patients can benefit from new innovative therapies at a reasonable price.

Facilitating debates on transparency of costs of research and development

We currently do not have clear evidence supporting claims that low pricing has led to shortages in the supply of pharmaceutical products. Occurring shortages seem to affect several countries at the same time, regardless of the product's price. Yet there are other cases where lack of access is related to pricing. In some countries, sudden, hefty price increases for off-patent medicines have made important treatments unaffordable, thus reducing patients' access.

There is also a relationship between the availability of new, innovative treatments and their price. Companies' market introduction practices tend to prioritize countries that accept higher pricing. Consequently, patients from smaller or lower-income Member States either are denied access to these medicines or need to wait for several months or even years for their treatments.
Recently, countries have gradually introduced managed entry schemes (MEA's) for high-priced medicines. These negotiations can cause (limited) delay in access to treatment patients, but there are also instances whereby MEA's prioritize or limit treatment to specific patient groups due to the product's price.

Many estimates of the costs associated to medicines' development and manufacturing have indicated that overall pricing practices include a significant margin of profit, which is not attributable R&D and production costs. As prices escalate, it is legitimate to question the degree of innovation and value offered by certain new, high-cost therapies. The sustained financial performance of pharmaceutical companies further underwrites the assumption that current prices do not accurately reflect the costs of production and research and development.
Furthermore, even though public funding often supports the R&D of many new pharmaceutical products, current pricing practices do not consider the social responsibility of companies to contribute to the sustainability and affordability of health care.

We welcome a joint debate on transparency with Member States and the EU Commission, to discuss a joint approach to introduce greater transparency about the costs of research and development within the European Union. One is only able to measure a fair return on public investment of funds used to support R&D if the actual costs of research and development are also known and available. This is an area where collective action is needed. We would like to refer to the WHO resolution on improving the transparency of markets for medicines, vaccines, and other health products that was also adopted by many EU member states, as well as to the Beneluxa statement regarding transparency as a key contributor to achieving sustainability of access to medicines.

Addressing selective market introduction

To enable equal access, the Netherlands advocates that pharmaceutical companies should be obligated to market medicines in all Member States once a centralized marketing authorization has been granted. At present, companies can select the Member States where they will market their

products. Such choices are frequently based on pricing strategies or expected turnovers. Equal access aims to create an equal playing field for patients and payers. The issue of selective market introduction does require a joint discussion of potential causes and solutions among Member States and the European Commission. Solutions should take potential adverse effects into account, e.g. price increases or limits to supply in smaller markets to comply with regulations.

Dealing with circumstances leading to market withdrawals

The Netherlands supports changes to the legislation to help maintain medicinal products on the market and to prevent shortages. These include the simplification of the procedure for variations, as well as the use of electronic leaflets enabling manufacturers to produce packages that can be used in all Member States, thereby introducing greater flexibility, but still safeguarding patient access to high quality, safe and efficacious medicines with the correct product information.

The costs involved in sustaining single-language packaging are high and the return on investment is low for the companies (as the market share is also low at national level). By pooling market-shares across various EU Member States, marketing authorisation holders could be stimulated to keep their product on the EU market.

We attribute the increase in market withdrawals due to manufacturers' decisions is to a combination of factors, among which efforts to manage or curb medicines' prices and existing regulatory burden and segmentation. When combined, such factors can create an unattractive market environment for some pharmaceutical products. Most notably, the legislative framework for lifecycle management is burdensome, from a regulatory and administrative perspective, lacking the flexibility to respond to digital, scientific and technological advances. Consequently, the manufacturing and control processes of products that have been longer on the market are not always updated to remain state-of-the-art, also due to high costs, and eventually some are withdrawn.

ENCOURAGING SUSTAINABLE PRODUCTION, USE AND DISPOSAL

Tackling residues of pharmaceutical products and addressing Antimicrobial Resistance

The current regulatory framework for pharmaceuticals and relevant policies require strengthening to address the emerging problem of environmental pollution and the emergence of antimicrobial resistance.

However, measures to be developed should not jeopardize access to medicines. Active pharmaceutical ingredients that are better degradable in the environment are also likely to be quickly degraded in the human body, leading to higher and more frequent dosing. This would not only negatively affect the environment but also increase the frequency and severity of side-effects.

The EU pharmaceutical strategy should have a clear link to the European One Health Action Plan against antimicrobial resistance, to the EU strategic approach to pharmaceuticals in the environment, and should support the work done by the relevant ad hoc working group of the Pharmaceutical Committee. It should also create a link between legislation on water, chemicals and the environment as well as the EU Green Deal's chemicals strategy for sustainability.

Pharmaceutical residues are introduced in the environment during production, use and disposal. Therefore, routine dialogue and collaboration between the healthcare, environmental, agriculture and water sector are key to create mutual understanding and efficient problem solving. 'Best

practices' need to be established and should be shared among Member States, as is currently done via the pharmaceutical committee ad hoc working group on medicines and the environment.

As to antimicrobial resistance, the priority would be to reduce their use, both through information campaigns (quick-win) and regulation (long-term). Raising the awareness of citizens and healthcare professionals about the appropriate use and disposal of medicines in general and antibiotics, in particular, is paramount. Labelling antimicrobial agents as prescription-only, while encouraging prudent prescription by physicians, could reduce the environmental impact at user level. A reduction in inappropriate prescription could be achieved by developing better point-of-care diagnostic tools that provide accurate information on whether antibiotics are required to treat the patient.

Objective, user-friendly information should be publicly available about the environmental risks of medicinal products. Patients can then make a joint informed decision with healthcare professionals about their treatment choice over other equivalent therapeutic options. In addition, transparency about environmental data allows the water-treatment sector to recognize and understand risks and to monitor pharmaceuticals accordingly in certain 'hot spots'. This would require agreement about the level of evidence of environmental risks, which would then be applicable to all medicinal products.

Transparency is key. Publication of consumption data for substances with an identified risk as well as for antibiotics supports prompter mitigation actions. In addition, transparency on environmental data allows the water sector to recognise and understand the risks and to monitor pharmaceuticals in certain 'hot spots' accordingly. The IMI-project PREMIER (Prioritisation and Risk Evaluation of Medicines in the EnviRonment) aims to build a risk-monitoring database for pharmaceuticals. Yet in order for the project to be successfully implemented, the developed database would need to fit into the regulatory framework.

We further support the principle that when a risk to the environment is identified in the Environmental Risk Assessment (ERA), adequate monitoring should be in place, combined with a regular review of its environmental risks. In addition, we support the EU Strategy on pharmaceuticals in the environment, which states that the environmental risk assessment and environmental expertise within the EU need to be improved.

Further, to prevent introduction of pharmaceuticals into the environment at production level, the regulatory framework of Good Manufacturing Practices (GMP) should be considered as a useful instrument and include standards for waste and wastewater management. In addition, production that is both environmentally-friendly and responsible should be stimulated, as well the number of specific groups of active substances, such as contrast agents, should be reduced in wastewater.

The development of personalised medicine and the improvement of diagnostic and delivery methods to reduce the use of pharmaceuticals should also be stimulated.

TAKING STOCK ON LESSONS LEARNT FROM THE CORONAVIRUS (COVID-19) PANDEMIC

In the Netherlands, long-lasting shortages were prevented by discussing solutions with pharmaceutical chain stakeholders, through close surveillance of the supply and the market, by increasing contacts with professional medical associations and patient organizations, and by carefully monitoring the availability of medicines frequently-used in intensive care units.

The Netherlands advocates European solidarity and cooperation with regards to the security of supply of medicinal products. Avoiding disproportionate stockpiling at Member States' level and preventing intra EU-trade barriers are examples of positive actions, where the EU Commission could play an important role.
The past months have shown that European cooperation and solidarity are vital in a pandemic of this magnitude. Exchange of good practices and information is essential. Both the Covid19 Clearing House and the EU Executive Steering Group on shortages could play a role in this. However, a clear division of tasks and competences is crucial. Moreover, the success of this type of cooperation relies on the willingness of all those involved in providing adequate and real-time information.
Joint European actions - complementary to actions taken at national and global level - on development, testing, purchasing and storage of vital medical products are key. The Netherlands advocates an evaluation of the Joint Procurement instrument to ensure it is fit for current and future needs.
The European consultation and coordination structures should be operational, clear and efficient so that Member States are aware and able to foresee upcoming initiatives, both at national and European level. In doing so, cohesion among Member States is enhanced and the risk of unilateral decisions minimized. Overlap of activities creates extra burdens on the system. More oversight and transparency for actions at European level would be welcomed. Likewise, greater coherence and coordination among the various structures at the EU level would be helpful.

SUMMARY OF PROPOSED LEGISLATIVE ACTIONS

1. To establish a definition for unmet medical need in the European Union linked to an established timeline, to be agreed beforehand
2. To review of the current legal framework for ATMPs and where necessary, introduce changes to facilitate and stimulate the uptake of these innovations.
3. To support changes to the legislation to help maintain medicinal products on the market and to prevent shortages. These include the use of electronic leaflets enabling manufacturers to produce packages that can be used in all Member States, thereby introducing greater flexibility, but still safeguarding patient access to high quality, safe and efficacious medicines with the correct product information.
4. The variation framework should be should be updated to:
    a) optimise use of digital solutions, such as SPOR and ePI,
    b) minimise administrative and regulatory burden,
    c) simplify procedures and processes,
    d) increase regulatory flexibility,
    e) better reflect actual risks for the different types of products,
    f) take account of scientific and technological advances in medicinal products, their production and post-authorisation lifecycle management.

    When considering measures to optimise the variation framework, it should be taken into account that supply chains are often global and that medicinal products are often marketed in more than one region. The EU variation framework should not hamper the application of scientific and technological advances in global supply chains and cross-regional products. In addition, reasons for underusing current opportunities for regulatory flexibility (design

space, PACMP) should be fully understood when looking for optimisation thereof. Finally, the work of the Regulatory Optimisation Group (ROG) of the HMA should be taken into account.

Quick wins

- Update the annex to the classification guideline to:
  - Reflect the actual risk related to a change to a particular product. Especially for biologicals and herbal medicinal products, several variations could be considered for downgrading.
  - Include the Article 5 recommendations.
  - Allow for more Type IA variations to be submitted through a database/portal as was done for a change to the QPPV or PSMF.
  - Enable the use of ePI.
  - Reflect the adoption of the Veterinary Regulation.
  - Correct any inconsistencies there may be between certain changes to the active substance versus the finished product.
- Prioritise variations that are essential for the safety and safe use of the product.

Long-term actions

- Update the Variation Regulation to:
  - Allow for greater regulatory flexibility as to respond to scientific, technological and digital advances and to stimulate enhanced CMC knowledge.
  - Optimise the use of grouping and worksharing.
  - Simplify processes and procedures.
  - Reflect the adoption of the Veterinary Regulation.
- Consider the option to have HMA and EMA have bigger ownership over the classification of variations, so that the process of amending is faster and less burdensome, thereby ensuring that the guideline is regularly updated as required.