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European medicines agencies network strategy to 2025

Protecting public health at a time of rapid change

Contents

1. Introduction: a Network strategy for a rapidly evolving healthcare environment

The European medicines regulatory network (EMRN) represents a unique response to the challenge of regulating human and veterinary medicines across a diverse group of countries. It includes the national competent authorities (NCAs) of the 27 EU Member States plus those of Iceland, Liechtenstein and Norway, who are responsible for medicines regulation at national level and also come together under the aegis of the Heads of Medicines Agencies (HMA) and the centralised regulator and coordinating body, the European Medicines Agency (EMA), within whose scientific committees sit representatives of those countries. The European Commission provides EU legal and supervisory authority to the Network's decisions.

These bodies have access to the knowledge of thousands of experts in multiple scientific and therapeutic fields and must work closely with stakeholder groups including patients and healthcare and veterinary professionals, health technology assessment bodies and payers, and the pharmaceutical industry and global regulators. Their duty is to ensure that patients, animals and the wider society have access to safe, high-quality and effective medicines, and so protect public and animal health, and the environment.

By working together under a common and agreed set of regulations and laws, and sharing resources, knowledge and expertise to maximise efficiency, they have created one of the world's leading systems for regulating medicines.

Such a complex enterprise inevitably requires detailed planning and coordination. While this is built into the Network's systems on a day-to-day, month-to-month level, it is also necessary to think about the longer-term direction of the Network and how we respond to the clinical, scientific/technological and social challenges it faces.

These challenges have never been greater. Developments in basic science, in medicine, in information technology and data analytics in particular, continue to pour forth at an astonishing rate, and the Network must respond to these. As well as ensuring access to essential older medicines, it must have the capacity and knowledge to regulate new types of medicine, making them available to patients with unmet needs while continuing to ensure that any risks are outweighed overall by the benefits. Globally, all societies must respond to environmental and climate change, address sustainability, and cope with the societal impacts of the so-called 4th industrial revolution. In this light, economic and political challenges also continue to face the EU and the wider EEA, not least the many challenges posed by globalisation and the global supply chains and just-in-time manufacturing processes on which modern society depends. These include dependency on manufacturing capacity and APIs/starting materials sourced from third countries and the need for increased preparedness for emerging health threats.

> The dangers of emerging health threats in particular have been made evident by the COVID-19 pandemic. As we have lived and worked through this situation, it has directly demonstrated the very real impact that such threats can have on society worldwide. Learning from this experience presents an opportunity to shape the future role of medicines regulation nationally and at the EU level, and enhance the partnership approaches that we need to ensure that we are proactively positioned to deal with similar emergencies.

On the broadest level the challenges we face go well beyond the remit of medicines regulation, and will need to be addressed by the EU and its Member States as a whole and individually: the EU's forthcoming Pharmaceutical Strategy for Europe will shape the policies to do this for human medicines,

thus setting the direction for the Network's response, and will continue to do so beyond the period covered by this strategy. In addition, other strategic initiatives are taking place at EU level to respond to the global challenges already referenced. However, more specific strategic planning on the part of the EMA and HMA is needed to ensure that the Network is ready to play its part and implement the actions needed to protect public and animal health going forwards, which is the role of the present document.

In the veterinary medicine area, the future will be shaped, *inter alia*, by the EU environmental strategy (European Green Deal) which is currently under discussion and which aims to improve public and animal health and the environment by a range of proposed measures, including significant reduction in use of chemicals in agriculture and of sales of antimicrobials for farmed animals and in aquaculture by 2030.

As the society that the Network serves continues to change and develop, we must also change and develop so we can continue our mission successfully, with the most efficient use of the resources and knowledge available to us. To achieve this will rely in particular on increased use of digital technology in our processes, to ensure data is standardised, collected and used intelligently. The Network should thus become a reference source for trusted data, able to reduce administrative effort, respond to challenges in a timely fashion and increase efficiency.

In 2015, the HMA and EMA came together to look ahead and develop an overarching European Medicines Agencies Network strategy for the coming 5 years, building on previous HMA strategy documents and EMA road maps. This strategy addressed 4 key priority areas (supporting development and availability of medicines for human health; increasing availability of veterinary medicines and reducing the risks of veterinary antimicrobial use; optimising the operation of the Network itself; and continuing to develop resource sharing and regulatory convergence at the global level) and was developed in consultation with stakeholder groups.

Building on the success of this previous strategy and the work carried out under its auspices, HMA and EMA are now planning for the next 5 years, in the shape of the proposals included in this document. These high-level goals and supporting recommendations will shape and feed into the detailed workplans of the Network's members in the coming years. As it strives to implement these, the Network will always attempt to follow its broad **guiding principles** of ***trustworthiness***, ***acting transparently***, ***communicating clearly***, ensuring the highest ***ethical standards***, and supporting ***environmental sustainability*** through reduced use of resources, emissions, degradation and pollution related to pharmaceuticals.

The Network recognises the need for change – more, it is eager to change, in order to fulfil its mission ever better. However, it cannot do this alone, and the strategy emphasises the importance of international collaboration and of communication and the need to engage ever more fully with our stakeholders and partners. This means sharing our respective views of the challenges ahead; showing that, even when methods and approaches change, ensuring the quality, safety and efficacy of marketed medicines remains our goal; demonstrating how the steps in the strategy will support improvements across the life cycle of a medicine; and inspiring a vision of a medicines regulatory system able to meet the challenges of the 21st century and provide EU patients with the medicines they deserve while continuing to protect them from unsafe and ineffective medicines.

2. Scope of the document

What does the strategy cover?

This document outlines six strategic focus areas for the joint Network strategy to 2025:

- Availability and accessibility of medicines
- Data analytics, digital tools and digital transformation
- Innovation
- Antimicrobial resistance and other emerging health threats
- Supply chain challenges
- Sustainability of the Network and operational excellence

Each of these is addressed in more detail below, with a discussion of the main challenges of each as the Network sees them, an identification of topic-related goals for each area, and, in Annex 1 of this document, proposals for high-level objectives that might form the starting point of actions to address these goals. These recommendations are necessarily at quite a high level. Detailed actions necessary to address the recommendations in each area will then be developed by the NCAs and EMA in their multi-annual work plans.

Some of these detailed actions will be largely or entirely the business of the national agencies, others will be primarily an EMA responsibility, while in many cases the work will be shared and will involve close collaboration. Having a joint strategy enables all three situations to be addressed in a coordinated and consistent way.

The strategy will be aligned with the broader **Pharmaceutical Strategy for Europe** being developed by the European Commission, as already mentioned, and its actions will seek to provide synergies with actions developed under the Pharmaceutical Strategy where their subject matter overlaps. Wherever matters of policy or potential legislative change for human medicines are referred to in this document these should be understood as identifying issues that could inform the broader Pharmaceutical Strategy, where the ultimate responsibility for such matters will lie.

The Network strategy will also take into account the Commission priorities for health, as outlined in President von der Leyen's Mission Letter to Stella Kyriakides, the current EU Commissioner for Health. As noted throughout the document, many of the lessons learned from the COVID-19 pandemic will be strategic considerations in the coming years, and will be sustained by the measures expected to be launched as part of the EU's 'EU4Health', and 'rescEU' programmes, including building a strategic pharmaceutical reserve of critical medicines, and encouraging API production in Europe. An Information Management Principles document will take into account Network business needs for digital transformation, allowing development of a roadmap and consideration of how these can be applied at Network and national level. As mentioned above, initiatives in related sectors will be considered where they overlap with the concerns of this strategy.

How was the strategy developed?

- During meetings in 2019, HMA members came to a consensus on 6 key focus areas for the new strategy and produced a concept paper discussing the challenges and how the Network might address them. This was then shared with EMA for reflection.

- EMA and HMA created joint working teams to address each of the focus areas, clarifying the scope and developing more formalised goals with supporting recommendations for action. These teams consulted external experts and partners as necessary and developed their proposals with an eye to alignment with other strategic considerations such as the EU Telematics Strategy and the priorities of the present European Commission.
- The conclusions of the 6 teams were distilled into a draft working strategy.
- An early engagement phase with stakeholders was organised within the limitations imposed by the COVID-19 pandemic; an early discussion with patient, consumer and healthcare professional organisations (PCWP/HCPWP) and a written consultation with industry, academia and vet stakeholders provided an opportunity for HMA and EMA to capture initial views for each theme of the strategy from these stakeholder groups.,The document will be subject to a 2-month public consultation during the summer of 2020.
- Comments from stakeholders and the public will be analysed and taken into account in a final post-consultation draft.
- Publication of the final strategy is foreseen for November 2020.

3. Strategic focus areas

The six strategic focus areas identified by the Network are discussed in more detail below. Inevitably, any such division of the issues is somewhat artificial, and some common and overlapping issues arise repeatedly under multiple themes, including the need for **pandemic preparedness** emphasised by COVID-19 and the more insidious effects of antibiotic resistance; the **impacts of innovation, digitalisation and big data** and the **need to ensure that the Network has the necessary competencies** to deal with them; the need for further, increased **collaboration and engagement with our stakeholders and downstream decision makers such as HTA bodies and payers** (particularly in explaining, preparing for, resourcing and managing **a shift to more post-licensing evidence generation** as the regulatory system evolves); the need to prepare adequately for the **implementation of new legislation**; an increased **focus on the supply chain, particularly to minimise shortages**, and on **environmental issues**; and a recognition of the importance of good **communication and transparency**.

3.1. Availability and accessibility of medicines

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down two main goals to be achieved within the strategy period:

1) Strengthen the availability of medicines to protect the health of European citizens, via:

- **efficient and targeted regulatory measures, made possible through an in-depth understanding the root causes of unavailability of patented and off-patent products;**
- **identification of possible challenges in implementing legislation, removal of national barriers, increased coordination of the EMRN, sharing and implementation of best practices including by the**

stakeholders and increased transparency are the essential steps towards this goal.

2) Optimise the path from development, evaluation through to access for innovative and beneficial medicines through collaboration between medicines regulators and other decision makers in the areas of:

- **evidence planning, including post-licensing evidence;**
- **engagement in review of evidence and methodologies, respecting remits of the various players;**
- **collaboration on horizon scanning.**

As a result of this work, medicines that address unmet medical needs should have broader and earlier access coverage.

Recommended high-level objectives to support these goals are given in the table in Annex 1.

Lack of availability of medicines in the EU/EEA, either because medicines are authorised but not marketed or no longer marketed, or due to supply disruptions, has been recognised by HMA and EMA as an area of great concern posing threats to patient health, animal disease control programs and sustainable livestock production.

This part of the strategy concentrates on availability and accessibility issues from the perspective of supply disruption/shortages [availability] and commercialisation/downstream decision making together with therapeutic challenges in small markets [accessibility]. Since ongoing implementation of the veterinary medicines regulation (Regulation (EU) 2019/6) will provide new measures for increasing the availability of veterinary medicines such as stimulation of the development of innovative veterinary medicines, including products for limited markets, and the improvement of the functioning of the internal market for veterinary medicines, the discussion in this section focuses primarily on these issues from the perspective of human medicines.

The causes of availability and accessibility issues of human and veterinary medicines are multifactorial and the solutions require actions at different levels involving all stakeholders: the broader policy issues will therefore form an important part of the Commission's Pharmaceutical Strategy for Europe. It is important to differentiate shortages caused by safety, efficacy or quality/supply chain issues from availability issues for commercial reasons, where political engagement may be necessary. Similarly, it needs to be acknowledged that commercial strategies, and pricing and reimbursement (P&R) considerations are major reasons for non-marketing of new medicines. Robust actions at EU level are necessary in order to adequately address the resultant health inequality and to ensure that all patients and animals across the EU can have access to medicines they need. Better understanding of the multifactorial causes and solutions is a precondition for an effective solution to the availability and accessibility of medicines. At the same time, it should be recognised that there might be unintended consequences: strengthening regulation of the supply chain, for example, may potentially come at the cost of reduced affordability, and would need therefore to be seen in a broader context than the regulatory remit.

Medicine regulatory authorities are only one of the many concerned players and operational measures taken by regulators cannot address all issues or solve all situations. In this context any strategy development should strengthen medicine regulators as important partners in facilitating and enhancing the work of other actors and stakeholders including HTAs and payers, political authorities and

international initiatives and organisations such as the OECD. The proposed EU Regulation on HTA, currently under the co-decision process, could provide an important instrument to implement and address several of the objectives and planned actions of this strategic area in relation to collaboration with HTA bodies. In terms of engagement with payers it is recognised that their heterogenous nature and varying responsibilities across the national healthcare systems in European Member States lead to more diversity in the areas for collaboration with regulators.

Supply disruptions/shortages (availability)

Increased collaboration within the EU is key to address shortages[1]. Medicine shortages are usually not isolated or limited to one market and cannot be solved through national measures alone. Thus, there is a need for coordinated action at an EU level to ensure effective measures and to avoid duplication of efforts. In addition, unilateral measures taken to address issues in one country, such as imposing medicines stockpiling and restricting export, can exacerbate shortages in other Member States. Therefore, there is an opportunity for a pan-European solution to the issue, which is a priority for the current Commission.

Lessons learned from the COVID-19 crisis, including the potential impact of repurposing medicines to treat a pandemic on their availability for their previous, authorised uses, will need to be taken into account (see also section 3.5.). Furthermore, matching supply data and forecast demand data of medicinal products at a network level by collecting information from various data sources (consumption data, e-prescription data, distribution data) will help prevent shortages in crisis situations, and beyond.

Investigation into the **factors causing medicine shortages** is essential as a first step to identify measures that may prevent shortages. In addition, there is a need to better understand the supply chain and different roles the various stakeholders play (MAHs, manufacturers, wholesalers, parallel distributors/importers, pharmacists). A particular focus on solutions for the generics/off patent segment is required since this is where most shortage situations are observed. This includes understanding how current regulatory requirements fail to encourage MAHs' oversight of the complex manufacturing and distribution chains and how regulatory costs impact on low-priced generics and older medicines vis-à-vis new pharmaceuticals. The system should also be as flexible as possible to facilitate access to smaller players such as SMEs and start-ups.

Other initiatives aimed at reducing barriers to national access or distribution may further improve the European or multi-national market for medicinal products. **Electronic product information (ePI)** is one such initiative and should be considered as a way to facilitate marketing of (newly authorised) medicines in all Member states and redistribution of medicines available in other Member states to countries experiencing shortages or where medicines are not marketed.

Increased transparency on the marketing status of centrally authorised medicines would give Member States insight on what is marketed in neighbouring countries. Marketing status data is to be included in the SPOR programme, facilitating its re-use and supporting greater transparency. This in turn should facilitate a more effective negotiation of pricing and reimbursement with MAHs. This information could also increase societal pressure on companies to place their products on the market since health care professionals and patients across the EU can see first-hand if a medicinal product is commercialised in their country, though in itself this would not guarantee marketing or accessibility. This information would also be very useful for HTA bodies.

[1] A shortage of a medicinal product occurs when supply does not meet demand at a national level. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-detection-notification-shortages-medicinal-products-marketing-authorisation-holders-mahs_en.pdf

There is also a need for increased transparency in the manufacturing and distribution chains. The growing outsourcing / off shoring trends throughout the manufacturing chain and the complex distribution environment pose a challenge to the quality and availability of medicines. Increased transparency would allow regulators to better monitor the supply chain and increase societal pressure on companies to keep control despite this fragmentation. This would complement measures at other levels to ensure traceability and oversight in the supply chain (see section 3.5.).

Good **communication** on these complex issues with patients, patient representatives and health care professionals is essential. The network should develop effective coordination and communication to foster trust and increase the chances of successful handling of a crisis.

Commercialisation/down-stream decision making (accessibility)

In order for European patients to gain access to best therapeutic options and innovative medicines, the Network needs to act at various points in the medicine lifecycle.

As part of the development of a broader EU model of horizon scanning (see 3.3.) it should play an active role in collaboration on **horizon scanning activities** such as the International Horizon Scanning Initiative (IHSI) for the benefit of the Network and HTA bodies/payers. It should also establish closer collaboration with HTA bodies during the **scientific advice procedures**, building on EMA/EUNetHTA cooperation, to ensure relevant evidence regarding relative effectiveness is available to support timely national decision making by HTAs/payers.

Increasing complexity and diversity of evidence means that further work is needed on how best to document and clearly **communicate the regulatory assessment** and the quality and robustness of the scientific evidence supporting the marketing authorisation. This improved communication and transparency should include highlighting the inherent risks of over- or underestimation of the real benefits and risks of a treatment, particularly when there are limitations and resulting uncertainties (e.g. orphan medicines, conditional marketing authorisations).

There is also a need to continue to collaborate with HTA bodies, and where appropriate, payers, on **pre-planning and generation of post-licensing evidence**. Such generation of evidence is largely only possible if products are reimbursed and used. It is important to ensure that all post-licensing evidence is made available to the regulatory network to facilitate timely follow-up of benefit-risk by regulators, including where payers enter into 'managed entry' or 'pay-for-performance' agreements. Such collaboration is also integrated with the Network's response to innovation (see also Section 3.3.).

Another aim is to develop better **metrics** as basis for cross-country comparison of accessibility by patients, including the impact of early access schemes. Metrics on accessibility should be developed in collaboration with other stakeholders and harmonised between member states.

From a veterinary perspective, as already noted the implementation of the **veterinary medicines regulation** will provide new measures for increasing the availability of veterinary medicines and these are not further developed in this theme.

Challenges

The challenges in this area include:

- the **complexity of the root causes** of shortages and the **role played by different stakeholder groups**. This includes the need to understand
  - how the intricacies of the **regulatory environment** itself (both at EU level and nationally) contribute to the problem, and looking at ways to address this

  - the risks the growing **outsourcing trends** throughout the manufacturing chain (including for APIs and raw materials) and the **complex distribution environment** pose to the quality and availability of medicines (see also section 3.5.).

- managing **resource impact of shortages on the Network** itself, in order to properly handle the increasing number of supply disruptions faced by NCAs on a daily basis.
- preventing the **erosion of public trust** caused by regular shortages and the inequality in healthcare across the EU due to non-availability of medicines in Member States
- finding the best way to **improve collaboration with HTA bodies and payers** in order to ensure that we provide coherent and consistent advice to developers, and manage the shift to increasing post-licensing evidence generation in a mutually acceptable way (see also section 3.3.). Engagement across decision makers is needed to establish agreement on development plans that can deliver "universal clinical evidence" and support better and more evidence-based prioritisation of innovative medicinal products within limited budgets; it is recognised that any strategic response might have other consequences (e.g. potential impact of reimbursement approaches on commercial decisions on marketing).
- ensuring a better alignment of the national **implementation of compassionate use** programmes in order to avoid competition with clinical trials, promote equity in access for patients during late stage development and improved utilisation of data from such programmes to support later decision making.
- how best to further **improve communication and transparency** about the evidence supporting regulatory decisions and the evaluation process, and on the marketing status of medicines

Interdependencies

In its planning, the Network will take into account a number of existing initiatives, including:

- Work programme of the HMA/EMA Task Force on Availability of Authorised Medicines.
- EMA/EUnetHTA work plan: https://www.ema.europa.eu/en/documents/other/ema-eunethta-three-year-work-plan-2017-2020_en.pdf
- HTA Network reflection paper: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/ev_20161110_co06_en.pdf
- EC proposal for a regulation on HTA: https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51_en.pdf
- International Horizon Scanning Initiative: https://ihsi-health.org/
- OECD activities with regard to access to medicines: https://www.oecd.org/health/health-systems/pharmaceuticals.htm
- Ongoing work on data standardisation and development of master data, e.g. implementation of international data standards like ISO IDMP across Europe and progress in implementing usage of SPOR throughout the Network, thus uniquely identifying products and manufacturers and allowing data to be re-used for multiple purposes
- Implementation of the veterinary medicines regulation, Regulation (EU) 2019/6, and its associated actions for improving accessibility of veterinary medicines and identifying veterinary medicines through a Union product database

The issues raised in this focus area are intimately connected to those related to globalisation and supply chain challenges (3.5.) and sustainability and operational excellence of the Network (3.6.) in particular. Those elements of the innovation focus area (3.3.) that relate to collaboration on post-licensing evidence generation will also be key.

3.2. Data analytics, digital tools and digital transformation

Strategic goals

Based on its environmental analysis of the strategic area (including the goal of creating a European Health Data Space set out in the European Strategy for Data), as well as the identified challenges, the Network has laid down five main goals to be achieved within the strategy period:

1)	**Enable access to and analysis of routine healthcare data and promote standardisation of targeted data**
2)	**Build sustainable capability and capacity within the Network including statistics, epidemiology, real world data and advanced analytics**
3)	**Promote dynamic regulation and policy learning within the current regulatory framework**
4)	**Ensure that data security and ethical considerations are embedded in the governance of data within the Network**
5)	**Map the use and needs of data analytics for veterinary medicines and support a streamlined approach across borders within the EEA**

Recommended high-level objectives to support these goals are given in the table in Annex 1.

The convergence of new treatments, treatment modalities, diagnostics, medical devices, wearables, sensors and connected health is generating enormous amounts of data and more and more routine healthcare data is captured in electronic format. With easy access to ever greater computational power and development of advanced analytics including machine learning, the digital wave is already impacting the medicines development process and healthcare systems. Principal sources of **real-world data** include electronic health records, claims data and data from registries. The use of real-world data to generate evidence for regulatory decision-making is already a reality and there is increasing interest in using big data and advanced analytics as a complementary source of evidence. The work at EU level on a European Health Data Space recognises the benefits of better access to such data to support public health and its use in the regulation of medicines and the strategy should be seen within this broader context.

In turn, this is promoting a paradigm shift from emphasis on pre-approval activities to strengthened post-approval activities using real world data. Clinical trials remain the foundational method of establishing the safety and effectiveness of medicines during the pre-authorisation phase. However, they do not fully reflect the real world, resulting in gaps between regulatory dossiers and subsequent clinical evidence needed by downstream stakeholders including HTAs, payers and ultimately clinicians and patients. This creates inconsistencies and suboptimal uptake and use of treatments, which digital techniques have the potential to address. The Network is thus seeing evidence from real-world data proposed as a way of complementing clinical trials and filling evidence gaps that cannot be addressed

through trials and this is reflected during discussions on medicines development, at marketing authorisation application and extensively in the post-authorisation phase.

Pre-authorisation, there is particular interest in real-world data as a complement to clinical trials for medicines to treat rare diseases, where a comparative randomised trial may be very difficult to perform. Real-world data may also support evidence on the natural history of the disease being treated and on populations beyond those represented in clinical trials. In the post-authorisation phase real-world data has an established place in the monitoring of product safety and there is interest in complementing this by monitoring product effectiveness in the authorised indication and monitoring performance in populations not studied pre-authorisation.

By viewing real-world data as complementary to clinical trials data the Network Strategy aims to benefit patients through better decisions based on more comprehensive evidence. The aim is that the planned generation of evidence from complementary sources can support decision-making not only by regulators but also by HTA bodies and beyond. Experimental evidence and data analysis techniques can be used to evaluate the impact of healthcare policy decisions and establish a feedback mechanism which can enable formulation and implementation of effective healthcare policies. This has been highlighted as one of the lessons learned from the COVID-19 pandemic, in which rapid collection and analysis of data to support communication and healthcare decisions by the Member States has been of vital importance.

To adapt to the industry and other stakeholders' ever-increasing use of **data and process analytics** and new **digital tools,** and to fully deliver our public and animal health mandate, we need to be able to utilise all available data and tools to generate evidence for better and more efficient regulatory and clinical decision making. Without this we risk a situation where the Network neither possesses the technology to receive and interpret such data, nor the competences or regulatory setting and procedures required to address developments in this field. This would curtail the Network's collaboration with third countries and other external stakeholders. Furthermore, the Network would not be able to reap the benefits of the transformation such as utilising artificial intelligence and reducing time spent on regulatory and scientific evaluation of marketing authorisation applications or related activities. Ultimately the EU could become an unattractive region for the global life science industry and innovative therapies and technology would not reach EU patients in due time.

This means we must ensure that the agencies of the Network continuously adapt to the rapid global evolution of digital healthcare systems so they can cope with the increased use of Big Data. including real-world data, advanced analytical platforms and new digital tools, and make best use of them themselves. It also emphasises the need for access to routine healthcare data and the requirement to promote standardisation of data reflected in the EC's policy on Open Data and the Public Sector Information (PSI) Directive.

In addition to the important contribution of healthcare data to the generation of evidence for regulatory decision-making, it is thus of utmost importance that the Network makes an appropriate **digital transformation** to modernise its processes and create a supporting digital infrastructure.. This implies a new way of leading and executing our work, with optimisation and automation of many of the Network's processes, and use of AI and digital tools in new ways to achieve our goals. This undertaking will constitute a fundamental transformation of the regulatory Network in line with disruptions seen in other sectors of society, e.g. the emergence of Uber, streaming services like Netflix and HBO and AirBnB that have completely transformed the market for transport, video renting and hospitality respectively. In the Network context, one can envision the use of patient level data in authorisation processes and 3D printed medicines as results of the digital transformation. This will require adequate resourcing, training and acquisition of new skills, further development of our existing sharing of best

practices (including learning from experiences in other sectors), and ways to enlist external support as required.

An important first step towards building sustainable capability and capacity within the Network is to map the main shortcomings of the Network and build a strategy and roadmap towards an ideal state of operation (see also the strategic elements referred to in sections 3.1. and 3.6.). It will be crucial that the potential impacts of ongoing legislative and business initiatives are understood and planned for, to ensure that we have the requisite tools and capacity.

The convergence of medicines and medical devices means that the authorities within the respective fields cannot do the mapping by themselves. It should be a joint effort by these authorities together with the HTA bodies – both at national and European level.

As the Network continues to evolve, it will need to take into account the **diverse level of digitalisation** across the EU member states as well as ensuring a more comprehensive digital interface to **optimise interaction** with our stakeholders, and EU citizens more widely. An important aim will be to provide fully digitalised deliverables (e.g. ePI, SPOR and IRIS) from the Network's own operations that can be used by others to promote a better use of medicines.

Providing digital support for **veterinary medicines**, for which the systems have historically been less well developed and resourced than for human medicines, will also be an important component of the strategy, and digitalisation of the relevant processes will be a significant element of the work to implement the 2019 veterinary regulation. Although the use of Big Data in veterinary medicine applications is not common, at least at present, the new legislation allows for the potential importance of Big Data, AI and block chain employment in pharmacovigilance, in the detection and reduction of antimicrobial resistance and in the monitoring of environmental impact.

Challenges

The challenges the Network faces in making such a transformation include in particular:

- the sheer increased **volume and complexity of data** ('Big Data')
- a **lack of regulatory standards, guidance and validation** for the use of patient-level healthcare data, artificial intelligence (AI) and machine learning
- a somewhat **static regulatory process** that is ill adapted to an increasingly dynamic environment in which technology and science, particularly in areas such as use of device data, real world data, adaptive algorithms etc., are developing faster than current regulations / guidelines
- **lack of technological capability and capacity** (hardware and software) within the Network to analyse patient-level healthcare data (including applicant's clinical data sets, images etc.) and support digital transformation.
- a **lack of required personnel and competences** within the Network for driving digital transformation, in areas such as AI/machine learning, assessment of advanced analytics, digital leadership, data and computer scientists. This could be developed in collaboration with the EU NTC.
- the **need to maintain public and stakeholder trust**; data and new technology must be used not only in accordance with legal requirements such as data protection legislation but also in line with societal values, ensuring a high level of data ethics within the Network via secure data management and high data ethical standards, and transparency regarding study results, statistical methodology and algorithms. In addition, we must be aware that digital transformation will bring

changes in the interdependencies between the Network and external stakeholders, including HTA bodies, authorities working with medical devices and training organisations.

- some stakeholders view **healthcare data as a commercial commodity** and this risks limiting the public and animal health benefits of real-world and big data. The Network should collaborate to promote access to, and analysis of, healthcare data where this is in the interest of European patients and of animal welfare. Access to and analysis of healthcare data should be facilitated through the development of the European Health Data Space.
- the need for mechanisms to ensure better access to, and wider sharing and re-use of, existing data and decisions in order to achieve more consistent regulatory outputs; this might include better access to electronic health records, claims data, patient registries and other data sources (taking into account issues that may be raised by GDPR requirements), moves to ensure interoperability of existing data sets on an international level, combining data to address specific validation needs of medicines agencies and appropriate infrastructure for access to and exchange of data, all of which could potentially form part of the work to create a European Health Data Space.

Interdependencies

The Network and its partners have already made considerable steps to understand some of the issues related to this theme and a number of existing initiatives will be taken into account in planning. These include:

- The ten prioritised recommendations of the Big Data Task Force
- Priority areas in the EMA Regulatory Science Strategy, notably on use of real world evidence
- The Commission's initiatives relating to digital transformation of health and care in the Digital Single Market and the European Health Data Space; in particular the communication on the European Strategy for Data, adopted in February 2020, which refers specifically to the activities of health sector regulators including medicine agencies
- Initiatives relating to regulatory optimisation (see strategic goals 1 and 4 in section 3.6.)
- Work to implement the veterinary medicines regulation, Regulation (EU) 2019/6, in relation to pharmacoepidemiology, signal detection and AMR, which will benefit significantly from use of Big Data and AI
- Implementation of international data standards like ISO IDMP across Europe and progress in implementing usage of SPOR throughout the Network; initiatives on e-submission and development of the clinical trial information system (CTIS) are also relevant
- The goals and objectives of the strategy should be mapped to the existing Telematics Application Landscape and Lifecycle Model in order to divine where investments in existing capabilities might be needed and where entirely new capabilities are required, ensuring that we promote re-use and long-lived capabilities/platforms

As with the wider digital transformation of society, digital transformation implies big changes to the way that the Network functions. As noted in the Introduction to this document, it will affect and underpin many of the initiatives reflected in other themes within this strategy, for example ePI and availability metrics (3.1.), many aspects of dealing with innovation (3.3.), and moves to improve the sustainability of the Network and operational excellence (3.6.).

3.3. Innovation

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down four main goals to be achieved within the strategy period:

1) **Catalyse the integration of science and technology in medicines development and ensure that the network has sufficient competences to support innovators in various phases of medicines development.**
2) **Foster collaborative evidence generation - improving the scientific quality of evaluations and ensuring generation of evidence useful to all actors in the lifecycle of medicines, including HTAs, and pricing and reimbursement authorities.**
3) **Enable and leverage research and innovation in regulatory science**
4) **Enhance collaboration with medical device experts, notified bodies and academic groups**

Recommended high-level objectives to support these goals are given in the table in Annex 1.

Advances from transformational research in biomedical science are bringing innovation and new treatment opportunities at an ever-increasing pace. Editing of the genetic code and functions of cells has already brought new and effective treatments against cancer and other major disease areas, while developments in Advanced Therapy Medicinal Products (ATMPs) also offer new opportunities to address unmet medical needs. Biomarkers identified from genomic, proteomic, metabolic and microbiomic data, as well as clinical and imaging data, offer the possibility to tailor treatments at a personalised level in a more targeted way (precision medicine). Such innovations may require novel manufacturing and delivery approaches including nanotechnology, 3D printing, decentralised *in-situ* manufacturing and greater use of medical device/medicinal product combinations and related diagnostics.

It is important that such innovations are handled in a way that ensures a patient-centred focus while protecting public health and availability of medicines. Capacity building and development of expertise on ATMPs at regulatory and HTA agencies is needed to cope with the increasing number of ATMPs being developed and seeking approval; knowledge sharing with international partners will be helpful in this regard. In the field of biosimilars, it is expected that regulators support and enhance the stepwise development of these products and further clarify the concept.

The importance of recognising innovation throughout the product lifecycle is acknowledged.

The increasing incorporation of digital tools, data standardisation and the consequent ability for improved evidence generation throughout the lifecycle of a medicine also offers an opportunity to better capture patient preferences during the evaluation process and make clinical development and regulation more cost-effective, potentially reducing the burden on healthcare systems. On the veterinary side alternative methods of evidence generation, for example through farm management systems, also offer similar opportunities. Regulators will need to support innovative and alternative approaches to data generation.

As with the digital arena (see 3.2. above) regulators need to adapt and evolve, developing the requisite competences for this quickly evolving environment. This is made more acute by social and

economic change: globalisation continues to make the surveillance of good practice related to drug development very challenging, greater environmental concerns remind us of the need for regulators to pay more attention to the international environmental impact of pharmaceuticals, and an aging population in EU countries emphasises the need for clinical studies in the elderly population. In this regard, initiatives in special/vulnerable populations, such as geriatric or paediatric populations, should be sought.

Regulatory science must advance in tandem with transformational research which significantly shifts existing scientific and treatment paradigms. This is necessary to ensure that innovation can be correctly, rigorously and efficiently assessed by the Network and made available as appropriate to patients, users and healthcare professionals to address their healthcare needs. The ultimate public health aim will be to ensure that regulatory science remains at the cutting edge so that the EMRN can deliver its fundamental mission of protecting human and animal health and facilitating the availability of medicines to patients and animals. (One relevant consideration will be whether innovative developments on the human side could also be applicable to veterinary medicines.)

Sharing best practice globally will also mean that the knowledge and expertise of the Network can contribute to public health on a wider stage. For unexpected emerging health threats (global crisis, epidemics, pandemics), it is crucial to seek early international collaboration and engagement, as has been shown by the COVID-19 pandemic. The pandemic has also emphasised the importance of being able to obtain sufficiently robust data quickly in a health crisis. Small, competing clinical trials are unlikely to be helpful in such a situation and there is a clear need to promote large, multicentre and multinational clinical trials to an agreed protocol and standard, so that good evidence can be provided to decision makers. Developing large EU investigator networks and investing in the public infrastructure to support such networks and trials ought to be a focus going forward.

An aim of particular interest for this strategy period is development of EU **horizon scanning capability** so regulators can become aware of innovation earlier and address questions from innovators at a much earlier stage. Regulators can thus play an important role in directing the development plans of innovations pursued by medicines developers, so as to help developers avoid major regulatory mistakes. Such horizon scanning activities should also consider synergies with other initiatives (see section 3.1.). A common model for horizon scanning is under development in the EU-Innovation Network and should be prioritised; global collaboration with other agencies is also needed. It is recognized that the different actors involved (regulators, HTA bodies, price and reimbursement authorities) may differ in the nature and timing of their information needs, so good communication on horizon scanning findings to ensure these continue to be met for all parties at different stages is essential. Other focus areas include:

- **how to classify complex, borderline medicines** and identify mechanisms to establish more convergence about borderline decisions at the strategy stage. All relevant stakeholders (NCAs, medical device authorities, EMA, European Commission and industry associations) must be involved; establishing an **integrated evaluation pathway** for the assessment of medical devices, in vitro diagnostics and borderline products for which specific expertise and collaboration between regulators is key
- developing **consistency and convergence in scientific advice** between national authorities, and exploring further synergies with HTA bodies and payers (building on the success of parallel scientific advice procedures);
- **supporting innovation and digitalisation in clinical trials** by strengthening the Network's expertise in handling more complex designs, including the use of data analytics and real-world data. Such innovation should go in parallel with a common regulatory framework and harmonisation within the EU/EEA; digital tools such as the clinical trial information system (CTIS)

and SPOR, and introduction of electronic submission and assessment processes will be important here but alignment on application of GMO requirements in the EU would also be required;

- working to **evolve the marketing authorisation paradigm** to a more dynamic model, in which authorities will be able to re-use data and use data analytical capabilities not only to validate the applicant's analysis at the time of assessment and initial benefit-risk analysis but repeat this at predefined time intervals post-approval;
- leveraging **collaborations on regulatory science with academia**, involving them in discussions about where research resources should be focused and engaging with academics and industry-based researchers involved in medicine development, to guide them through the regulatory pathway. As an example, early development of ATMPs usually takes place in academia making regulatory advice at an early stage necessary. Relevant training in innovation areas must be developed in close collaboration with these groups;
- fostering innovation in vaccines development through collaboration between regulators and other stakeholders such as policy makers, developers, academia, industry and National Immunization Technical Advisory Groups (NITAGs) may help accelerate the complex and challenging development, approval and post-marketing monitoring of the next generation of innovative vaccines including those for pandemics such as COVID-19.
- contributing to the development of regulatory and scientific guidelines to facilitate new innovative treatment options and cope with emerging challenges;
- addressing environmental aspects of innovation without jeopardising either support to medicine developers and protection of public health.

The Network should also further strengthen its engagement with public-private partnerships such as Horizon Europe during the strategy period.

All of these focus areas come with associated challenges (see below).

Challenges

Focusing on the areas of innovation above also foregrounds a number of challenges:

- as increasingly complex medicines are developed that converge different technologies or apply 'platform technologies' in multiple ways to promote and protect human and animal health, there is a lack of **consistent EU-wide rules** on whether a borderline product should be considered a medicine, or a medical device, and decisions may therefore vary between Member States. To support such developments, consistent application of rules should be a goal during the strategy period, ensuring consistency throughout the lifecycle of the product. Strong alliances with experts from medical device authorities and others (Member States, European Commission, EMA, industry associations) will need to be sought. In addition, a better understanding of medical device regulation and their mechanism of actions by regulators will be helpful.
- innovations in **patient-centred healthcare**, and **precision/personalised medicine** often do not fit properly into existing regulatory systems. This can range from treatments that target stratified populations (biomarker-led medicine) or different stages of the disease, to the use of individualised treatment such as modified autologous cells. Protecting public health while providing a regulatory environment that can support technological progress such as the increasing use of 'omics'-based biomarkers to support precision medicine is key if EU patients' needs are to be better addressed with new, safe, effective and clinically appropriate treatments.

- development of innovative and precise medicines, for example with the success of incentives for medicines for rare diseases, has led to more conditional marketing **authorisations based on sometimes very limited evidence**, and this is likely to increase with the trend for more targeted medicines in which new biomarkers result in splitting larger indications into smaller ones. The resultant need for confirmatory evidence about efficacy and safety of such products puts a lot of pressure on **post-licencing evidence generation**, which is needed not only by regulators, but also by HTA bodies and pricing authorities. Meeting the challenge is likely to mean adapting the marketing authorisation system to reflect that the initial marketing authorisation is only the first step in the process of evidence generation about the benefits and risks of the product. It is recognised that this may lead to situations where products are withdrawn from the market because efficacy could not be confirmed by Marketing Authorisation Holders after initial marketing authorisation was granted.
- new and **innovative clinical trial designs and methodologies** are already challenging the system. Complex designs such as umbrella trials and basket trials require advanced biostatistical and data analytical understanding and recruitment of patients may also change with the use of new technologies such as social media or AI to identify eligible study participants. New sources of data, such as health apps, electronic health records, wearables etc. are already being used to capture data during clinical trials, and companion diagnostics being developed and there is a need to adapt the Network's IT landscape to handle innovative products including addressing the potential for products developed by or incorporating AI/machine learning. Challenges include **validation** of such devices and tests, **data ethics and GDPR** considerations (see also 3.2 above). An increased need for interaction with competent authorities for medical devices is also foreseen. The commercialisation of data (a so-called "data market") may be a barrier to regulatory access as noted in the challenges under section 3.2. above.

  In addition, cybersecurity issues may also emerge.
- the regulatory system needs rapid **access to appropriate expertise** to ensure adequate, fit-for-purpose and effective regulation and so that the latest scientific and technological knowledge can be built into medicines development where it benefits public health. This requires closer collaboration on an international level with academics, research centres and infrastructures to ensure that such expertise is present in the ongoing dialogue between regulators and developers at all stages of the process. In the absence of the required expertise there will be a need to identify **training needs**.
- the need for stepwise implementation of a **coherent view of innovation and scientific advice provision**, agreed and built into all pre- and post-approval regulatory activities as well as subsequent HTA and pricing and reimbursement (P&R) decisions for the entire life cycle of medicines. The proposed EU Regulation on HTA, currently under the co-decision process, could provide an important instrument to implement and address collaboration with HTA bodies.
- stronger **alliances with relevant regulatory global partners** are needed to work together as we develop our approach and response to the challenges from innovation.
- innovative products will create new requirements for **storing data and maintaining the data lifecycle** of medicinal products at national and European level

Interdependencies

Existing initiatives that need to be taken into account in this area over the strategy period include:

- the project STARS (Strengthening Training of Academia in Regulatory Sciences and supporting regulatory scientific advice) supported by the DG Research and Innovation, which aims to create a

curriculum for academic groups on the most important regulatory science aspects of clinical trials (both EMA and NCAs have a common interest in close liaison with academic groups and a stable collaboration model with its respective roles should be implemented)

- EMA Regulatory Science Strategy to 2025 (plus any related ongoing action plans)
- EU Cancer Action Plan (under development)
- Horizon Europe and IMI Research Agendas
- Ongoing initiatives on horizon scanning such as the common model under development by the EU-Innovation Network or TISP project in collaboration with EUNetHTA or collaboration within ICMRA.
- Repurposing project under the auspices of the Commission Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP")
- the new Medical Device Regulation
- Simultaneous national scientific advice project
- Parallel consultation between Regulatory Authorities and EUNetHTA
- EU-IN work plan
- INNO group

Again the effects of innovation will be felt in many areas of this strategy, including in particular the sections on data analytics, digital tools and digital transformation (3.2.), globalisation and supply chain challenges (3.5.) and sustainability and operational excellence (3.6.), as well as its impacts on availability (3.1.).

3.4. Antimicrobial resistance and other emerging health threats

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down six main goals to be achieved within the strategy period:

1) **Provide high quality information on antimicrobial consumption and surveillance data on antimicrobial resistance in animals and humans in support of policy development.**
2) **Contribute to responsible use of antibacterial agents and effective regulatory antimicrobial stewardship in human and veterinary sectors by putting in place strategies to improve their use by patients, healthcare professionals and national authorities**
3) **Ensure regulatory tools are available that guarantee therapeutic options (with a focus on veterinary medicines) while minimising impact of antimicrobial resistance on public health and the environment**
4) **Define pull incentives for new and old antibacterial agents, including investigating support for new business models and not-for-profit development**

5) **Foster dialogue with developers of new antibacterial agents and alternatives to traditional antimicrobials, to streamline their development and provide adequate guidance in both human and veterinary medicine**

6) **Improve regulatory preparedness for emerging health threats**

Recommended high-level objectives to support these goals are given in the table in Annex 1.

In the light of the COVID-19 pandemic and the suffering and disruption it has caused on a global scale, the importance of emerging health threats caused by previously unknown pathogens has been underlined, and will have an important influence on this strategy and the broader policies within which it sits. However, while applying the lessons learned from the pandemic it is important not to lose sight of a more insidious health threat, namely that of **antimicrobial resistance** (AMR).

AMR is one of the major global threats to public and animal health. It is considered to currently cause about 33,000 human deaths per year in the European Union (EU) alone while global estimates amount to approximately 700,000 human deaths annually. If the emergence and spread of AMR progresses without restraint, the annual number of deaths worldwide is expected to increase to millions, making AMR a more common cause of death than cancer by 2050. AMR carries a heavy economic cost already, which is considered to amount to EUR 1.5 billion in the EU alone due to health care costs and productivity losses.

AMR demands a "One Health Approach", requiring collaborative multidisciplinary efforts involving legislators, regulators, physicians, veterinarians, academia, the pharmaceutical and the food industry as well as the agricultural and importantly, as highlighted by a number of studies, the environmental sector.

Increased consumption of antimicrobials leads to increase in antimicrobial resistance. The risk grows higher with misuse of antimicrobials including inappropriate use, dosing errors, duration of administration or excessive use of broad-spectrum antimicrobials. In order to maintain effectiveness, it is important that the right antimicrobial is selected and that they are only be used in cases where their use is justified. Reduction of antimicrobial use (e.g. by infection prevention, vaccination and promotion of responsible use, avoiding misuse and overuse) is key to addressing the risks to public and animal health. Also important are efforts to discover and develop new antimicrobial agents and alternative therapeutics. Despite the increase in AMR this latter component is currently rather lacking, with limited engagement from the pharmaceutical industry and the financial failure of some smaller players. New approaches are needed to ensure availability of, and access to, critical antimicrobial agents (including maintaining EU production capacity for older, critical antimicrobials) and the development of alternative preventive and therapeutic approaches.

Beyond AMR, the emergence and re-emergence of infectious diseases requires a global collaboration to develop effective and timely responses. Such health threats will often be best addressed in a One Health approach for which the experiences in addressing AMR provide valuable reference points.

Key areas for the Network in the forthcoming years include encouraging **appropriate use of antimicrobials** (including during pandemics) and supporting adequate stewardship and surveillance of resistance in all Member States as a most urgent measure to addressing antimicrobial resistance in the short term, to preserve efficacy of the currently available medicinal products. This may include

- continuing to **harmonise and modernise the product information** for longstanding antibacterials to support appropriate use

- publishing interpretative **criteria for susceptibility testing** following EUCAST (including VETCAST) deliberations
- helping to guide therapeutic decision making by **classifying antimicrobials** in consideration of their human and veterinary therapeutic importance and availability of therapeutic alternatives
- ensuring data quality and standardisation of data relating to availability and consumption of medicines.

Next, it is crucial to further and more effectively **support research** into new antibacterial agents and **incentivise development** of new options, including **therapeutic alternatives to antibiotics**. Regulators cannot tackle the problem alone, but can guide developers on regulatory requirements, including platforms for dialogue such as PRIME and ITF, and supporting development of new veterinary antimicrobials through preliminary risk profiling at the pre-submission stage. Although much of the Network is not directly involved in issues of reimbursement, it should be supportive of **new business models** to incentivise the private sector (while making sure there is no overuse or misuse) by decoupling sales volumes from return on investment and development of pull incentives for successful products. The potential contribution of not-for-profit organisations should be further investigated.

Continued collaboration with other actors and stakeholders will be vital, including with **WHO** to review the pipeline of investigational antibacterial agents and essential "old antibiotics", with **HTA bodies** to reflect on options for a specific value assessment framework for antibiotics for use in humans, and in various **international forums** to ensure harmonisation, such as the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) and tripartite meetings.

Collaboration and joint planning will also be vital in ensuring that the Network and its partners are as prepared as possible to handle **emerging health threats** and emergencies such as pandemics, as referred to at the start of this section and throughout the strategy. The unprecedented COVID-19 pandemic due to novel coronavirus ((SARS-CoV-2) is a dramatic current example of the public health response needs and the potential impacts. Experiences with COVID-19, Ebola, Zika, SARS/MERS and a decade ago with the influenza pandemic have shown the importance of emergency preparedness and having **public health advice and counter-measures**, in particular vaccines and antivirals, available in a timely manner.

To ensure this, regulatory decisions and pathways for appraisal of medicinal products both in inter-epidemic periods and during outbreaks require continuous refinements of the regulatory science and regulatory tools and procedures. Such health threats may again be best addressed in a One Health approach using global collaboration with other actors and stakeholders to develop an effective and timely response.

Importantly, **new approaches to estimate efficacy** of medicinal products for human use in such a case, via animal models or human challenge models, need to be further explored before outbreaks occur, as do similar models for medicinal products for veterinary use. Clinical studies using human challenge models raise the need of agreement around **requirements for clinical trial approval**, in particular minimal requirements of the quality of the challenge material (e.g. level of GMP compliance), and must take into account the ethical dimension of any approach. The GMO framework would also require a broader agreement with respect to both human challenge studies and testing of vaccines in emergency settings. The route for **use of investigational agents in the context of emergencies** would benefit from a more harmonised approach across the EU together with the possibility of stockpiling relevant medicinal products for use across the Union.

Another area of discussion is around the use of **platform technologies** that could speed up availability of vaccines and biological products in the face of unpredicted emerging pathogens. The extent to which the establishment of a platform technology can alleviate and accelerate regulatory decision needs to be further defined as part of the preparedness activities.

More broadly, regulators should do what they can to **explore alternative approaches** to treatment of infectious diseases and combatting development of resistance, such as bacteriophages, monoclonal antibodies, vaccines for healthcare associated infections, and combination therapy, including options for veterinary medicine. This may require **development of appropriate regulatory pathways** for, e.g. customised use and use of phage libraries or development of microbiome products. Regulation will also need to support the choice of appropriate therapies in human and veterinary medicines through use of rapid **point of care diagnostics**.

A major tool in tackling these challenges on the veterinary side will be the **implementation of the veterinary medicines regulation**, which will, among other key activities, support **expanded collection of sales and use data** for antimicrobials by animal species, providing information on the use of antimicrobials in animals across Europe to support national policies. Through EMA the Network will also provide **scientific advice** to the Commission in areas such as designation of antimicrobials reserved for human use and restrictions to the prescribing cascade for antimicrobials, as well as developing fit-for-purpose **guidelines** to support regulatory decision making. In order to address the potential impact of environmental residues of antimicrobial medicines on the emergence and spread of AMR, we will explore the **Environmental Risk Assessment** (ERA) in more depth.

Challenges

AMR is addressed by multiple national, European and international strategies following the One Health approach. This complexity, and the requirement of a deep intersectoral collaboration of a broad range of stakeholders, pose significant challenges in developing a strategy for this area:

- Thus far, the particular involvement of regulators has been limited. Joint efforts of human and veterinary stakeholders have been scarce and often hampered by conflicting sectoral aims. Ambitions and measures on AMR have thus appeared more aspirational than realistic in many instances. The Network **needs to foster multidisciplinary intersectoral cooperation, dialogue between human and veterinary stakeholders and increased involvement of regulators**.
- National action plans on AMR are tailored to a certain degree to participating stakeholders, regional epidemiological situations and specifics of national surveillance systems of AMR, AMU (antimicrobial use) and antimicrobial sales. **National One Health approaches thus vary**, leading to differences in national implementations of targeted measures (e.g. stewardship programmes and benchmarking). However, concerted intercountry action is considered a key component in tackling AMR. The Network should leverage national efforts, to foster their harmonisation and to further refine a targeted common European approach on AMR. An increase of cooperation and communication across the Network would also help further streamline activities related to emerging health threats from infectious diseases.
- Further **international coordination and solidarity** are critical. The Network must build on successful international initiatives such as the tripartite meeting scheme between the EU, the US and Japan, TATFAR and the Codex Alimentarius Task Force on Antimicrobial Resistance (TFAMR). The same need for coordination and solidarity with regard to emerging health threats has been made evident during the COVID-19 pandemic.

- Regarding the collection, reporting and quality of data on AMR and antimicrobial use in particular, we see **potential to further harmonise, standardise and extend national surveillance** with EMA having a key role in analysis and reporting of such data for the veterinary sector.
- From a regulatory view, **the size of the problem of AMR has often been insufficiently recognized and addressed**. As a Network, we consider the **need to identify current blind spots** as an opportunity for new approaches to address AMR – taking into account the specific nature of anti-infective medicines (antimicrobials, vaccines, alternative therapies, etc.) and their requirements for specific marketing and post-marketing authorisation requirements, prescription status specification and Health Technology Assessment (HTA) compared to conventional medicinal products. **Adequate resources must be provided** for the necessary actions, e.g. for the review of SmPCs of old antibiotics.
- **Antimicrobials have to be affordable on a sustainable basis** which calls for an optimisation of use, stocks, the supply chain (including risk analyses) and incentives for maintaining manufacturing of old antibiotics together with health care and dispensing systems that ensure access to antimicrobial medicines and alternatives thereof. In this regard, the Network must focus on the **end-to-end supply chain** (see also section 3.5.) and on **how to incentivise manufacturing capability** while safeguarding responsible use.
    - Access has to be ensured, while de-linking return on investment from the volume of sales.
    - The economic case must be made for sustainable research and development of anti-infectives, vaccines, diagnostics and innovative products for humans and animals.
    - This correlates with the investigation and establishment of a transparent regulatory framework for alternative preventive and therapeutic approaches such as bacteriophages, peptides, monoclonal antibodies or microbiome products.
- The potential interaction between the problem of AMR and that of pandemic management should be borne in mind: as noted by WHO, it will be essential that antibacterials are used appropriately in patient management, to avoid exacerbating AMR.

Interdependencies

Major initiatives on pandemic preparedness are being launched or strengthened in the wake of COVID-19 and any actions proposed in this strategy will be aligned. Similarly, a number of initiatives on AMR are already existing and will be taken into account for the development and definition of specific objectives and actions on AMR.

- The veterinary medicines regulation, Regulation (EU) 2019/6, which provides additional tools for regulators
- the EC Action Plan and Council Recommendations on AMR, aspects of which have already started being implemented by EMA.
- the EMA Regulatory Science Strategy to 2025, which includes specific actions on AMR by promoting the responsible use of antimicrobials and their alternatives.
- Recognising AMR as a global threat, the Network's strategy and actions takes into account guidance and information developed by international organisations, such as UN, WHO, OIE, FAO and OECD. As noted above, the Network will build on the existing successful international initiatives such as TATFAR and TFAMR.
- the implementation of SMS (standardised substance identification) and the EU-SRS database in Network activities and IT systems.

- The initiatives on preparing for emerging health threats proposed by the EU under the umbrella of the EU4Health and RescEU programmes.

Some of the work involved in this strategic area will be closely linked to initiatives in other areas of the strategy, notably in the areas of availability and accessibility (section 3.1.), the use of new data analytics and tools (3.2.), innovation (3.3.) and supply chain challenges (3.5.).

3.5. Supply chain challenges

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down five main goals to be achieved within the strategy period:

1)	**Enhance traceability, oversight and security in the human/veterinary medicine supply chain from manufacturing to importation and final use of active pharmaceutical ingredients (APIs)**
2)	**Enhance inspector capacity building at EU and international level to address the problem of APIs, new technologies and continuous manufacturing**
3)	**Reinforce the responsibility for product quality by harmonising and reinforcing guidance to facilitate a coherent approach to the standards by regulators and industries**
4)	**Encourage supply chain resilience and review long-term risks resulting from dependency on limited number of manufacturers and sites, to ensure continuity of supply and availability of medicinal products.**
5)	**Analyse the possible implications of new manufacturing technologies in order to regulate the new supply chains needed to manufacture and distribute new types of medicinal products for human and veterinary use.**

Recommended high-level objectives to support these goals are given in the table in Annex 1.

Public and animal health protection depends on a continuous strengthening of supply chain security, both to ensure presence and continuity of supply of the high-quality medicinal products that EU citizens expect, and to permit the entry of new products and technologies while ensuring that their manufacture is carried out and supervised to an appropriate standard. Given the number of actors involved, effective communication and engagement with stakeholders at all levels of the supply chain is essential to achieve this.

Today, the **supply chain** of medicinal products throughout the product lifecycle, from development through to commercial production is **global and increasingly complex**. Active substances may be manufactured outside the EU (e.g. in China or India), further formulated and packed or repacked in other third countries or within the EU.

Globalised supply chains and markets underline the need for **extended supervisory oversight** of supply chains, especially active substance manufacturing, through international co-operation and collaboration based on existing (such as with EDQM) and new initiatives.

Hence, **inspector capacity building** will be key to any strategy. Within the EU, the complex development, manufacturing and distribution channels continue to require supervision by EU NCA's. Internationally, EU authorities are working with third country authorities either through bilateral or multilateral **international co-operation frameworks** in order to build confidence and trust in order to increase reliance on each other's supervisory systems. Building on these initiatives is key to the most efficient use of inspection resources increasing the breadth of supervision, as well as improving the manufacturers' own understanding of their responsibilities. For example, the network should make optimum use of mutual recognition agreements (**MRA**s) through expansion of scope to include more product categories where appropriate or recognition of inspections by MRA partners in third countries where GMP certificates are available from the MRA partners.

Training inspectors and gaining experience with the implementation of the delegated regulation to the **Falsified Medicines Directive** will be important elements in responding to challenges in the security of the supply chain .

Enhancing linkages in medicinal **product and supply chain information** such as records in EudraGMDP, in the Article 57 Database and in the EU product database for veterinary medicines as well as in EMVS will provide a valuable information source for authorities.

The unexpected presence of N-nitrosamine impurities in angiotensin II receptor blockers and other products subsequently identified, has raised concerns about the quality of medicines and the controls applied by API manufacturers, finished product (FP) manufacturers and Marketing Authorisation Holders. The lessons learned from the nitrosamine incident may lead to a **more tailored supervision of API manufacturers** through assessment and inspection of their API development and risk management practices in technology transfer. There is an opportunity to **increase routine assessor-inspector joint inspections** within the current framework especially for pre-approval inspections of API facilities and in the context of the implementation of the EU-US MRA. Utilising the different SPOR services will maximise the benefits of the assessor of inspections collaboration and contribution of non-EU regulators like FDA.

The current regulatory framework establishes a basis to **reinforce the responsibilities for product quality** and conduct of the actors within the supply chain. The competences between authorities, especially as regards how GDP activities are authorized and supervised locally, are fragmented. there should be consistent and comprehensive implementation of the current GDP principles in all Member States to ensure the integrity of the supply chain. In addition, there could be a **review of current EU GDP guidelines** for human medicines and API's to establish if they remain sufficient to regulate the complex distribution channels in the EU (and those being developed for veterinary medicines should be considered for possible alignment). **Promoting synergies among GDP actors** is needed to support the development of consistent GDP guidance. The harmonisation of GDP guidance would facilitate a coherent approach to the standards and implementation of resource-effective inspection programmes.

Conversely, GMP activities are harmonised at EU and international level but **GMP guidance** also requires work in some areas. The current GMP for ATMPs covers the batch release process in cases of decentralised manufacturing; however there is no analogous regulatory guidance for other medicinal products including:

- Gases, e.g. nitric oxide, oxygen;
- Blood products, e.g. modified platelet rich plasma;
- Small molecules, e.g. 3D printing.

The lessons learned exercise launched as a result of the nitrosamine incident may lead to further developments in GMP and Quality guidelines aimed at MAH's and reflecting on the importance of

thorough development studies and of process and product knowledge and that manufacturers should ensure implementation of advanced quality management systems. One aim would be to increase awareness of the importance of strengthening oversight of the entire supply chain, and extending to the development phases, including clinical and non-clinical testing. Implementation of the 2019 veterinary medicines regulation will lead to new delegated regulations for GMP for **veterinary medicines**, GDP for veterinary medicines, and GDP for active substances, and further guidance, especially in relation to GMP regulated activities will be published during 2020.

Disruption in pharmaceutical supply chains poses risks to the **continuity of supply and availability of medicinal products**. This has been emphasised by the effects on global supply chains seen in the unprecedented COVID-19 pandemic.

Asking for inclusion of risk-assessment evaluations from the manufacturers of the API and finished product (FP) in the application for a marketing authorisation, regarding the supply capacity and their respective measures for mitigation of any potential disruption, would strengthen supply chain resilience. Such a risk assessment should include whether to procure the active substance (and starting materials in general) from different sources and various regions of the world. At the time of writing, the COVID-19 pandemic has also highlighted that the repurposing of already authorised medicinal products to treat a new disease can undermine the market availability of such medicinal products for their authorised indications.

There may be future **developments in the regulatory framework encouraging supply chain resilience** to ensure continuity of supply and availability of medicinal products through measures which favour the manufacturing in the EU in order to decrease the dependency on third countries and promote diversity of suppliers and contribute to the EU's strategic autonomy.

Along with the impacts of globalisation, industry is currently experiencing a technological leap that has been termed the 4th industrial revolution or Industry 4.0 (**Pharma 4.0** in the context of pharmaceuticals). This includes advanced digitalization within factories, and the combination of Internet technologies and future-oriented technologies in the field of "smart" objects (machines and products).

Technology advances in research and development are leading to advances in automation and alternatives to traditional scale manufacturing and purification techniques leading to smaller batch sizes and faster production times that proponents contend can ultimately be combined in a closed, easy-to-operate, tabletop-sized machine with integrated production and purification that could be used in for example a hospital pharmacy or operating theatre (**decentralised manufacturing**) or even mobile clinics to provide **customised products** designed to address the needs of an individual patient.

Regulators can help **support a competitive EU-based manufacturing base** able to implement Pharma 4.0 manufacturing models (with all that means to the supply chain) through engagement in ICH and development and implementation of appropriate guidelines, e.g. Q9 (revised), Q12 (new), Q13 (new). There may also be further **developments in GMP and Quality guidelines** aimed at regulating the new supply chains needed to develop, manufacture and distribute new types of medicinal products. Future potential legislative initiatives may also result in changes, particularly at the interfaces between tissues and cells and organs, to the current **framework for Substances of Human Origin** (SoHo) that may lead affect the way plasma or tissues as a starting material for medicinal products are currently regulated and inspected.

The degree of automation and big data that are foreseen as needed to support Pharma 4.0 will also mean that the application of Quality Risk Management (QRM) to the **design and validation of computerised systems and data analysis and forecasting methods** will be very important. It will

be vital to **equip EU inspectors and assessors with the skills, training and relevant tools** to inspect and assess the new technologies. Considering the emergence of data driven paradigms, there is a further need to develop EU-level **data integrity guidance** by adaptation of existing published Q&A's into Chapter 4 and Annex 11 of the GMP Guide in collaboration with WHO and PIC/s.

A key element of the new paradigm will be the move from traditional batch-based manufacturing to Continuous Manufacturing (CM). It will be important to **avoid regulatory barriers or lack of harmonisation** between regulators if industry is to innovate and develop in this area.

Challenges

A number of obvious challenges must be faced if the Network is to secure and protect its supply chains.

- It seems likely that the **EU will remain dependent on India and China** as major sources of generic medicines, biosimilars and API's. In addition, there are indications that even more third countries could become players in the supply chain. The COVID-19 crisis has illustrated that being dependent only on **production located in specific spots might pose a risk to continuity of supply**. Medicinal products, such as antibiotics and vaccines, are increasingly manufactured outside the EU. Longer supply chains and supply chains relying on single or limited source manufacturing and just in time production remain vulnerable to disruption. Older niche products that remain important to public health may be vulnerable to **commercial pressures that impact availability** and there will be a need to build the **EU's strategic autonomy**. Repurposing of authorised medicinal products might entail their scarcity for the authorised indications. On the other hand, new treatments to fight epidemics, especially promising ones, might not be promptly available to patients on an equal basis across the different EU regions.
- The potential for presence of **falsified medicines** in the supply chain has also been amplified by globalisation leading to a substantial increase in reports in various countries in recent years.
- As noted, there is a **need to enhance existing capacity building initiatives** in the EU to support GMP, GCP and GDP inspector capability and capacity. There is also a need to enhance existing capacity building initiatives to support GMP and GCP inspector capability and capacity in third countries.
- At the moment, **regulatory barriers** or lack of harmonisation of regulatory approaches is seen as a significant barrier to industry innovation and take up of new models such as continuous manufacturing. Sustainable harmonised GMP guidance and supervisory procedures via GMDP IWG will be needed to provide a level playing field and a stable EU GMP regulatory environment with predictable outcomes, to allow for investor certainty and to attract inward investment in manufacturing.

  The implementation of the **veterinary medicines regulation** will lead to new delegated regulations for GMP for veterinary medicines, GDP for veterinary medicines, and GDP for active substances. Associated guidance such as EU GDP Guidelines for veterinary medicines and API's is not available and should be developed. The emergence of **veterinary novel therapies,** basically veterinary ATMPs, has highlighted that the current GMP framework does not provide sufficient guidance in this area and further work is needed.

Interdependencies

Existing initiatives and programmes with which there are synergies or with which this Strategy will need to be aligned include:

- Work to extend the EU-US Mutual Recognition Agreement to the area of veterinary medicines, vaccines and blood and plasma; this will be an important milestone once achieved. More informal and less-resource intensive mutual reliance initiatives may also become more significant in the future to provide more agile and flexible approaches
- Information sharing initiatives such as the International API programme, the 'Pilot programme for international cooperation in GMP inspection of manufacturers of sterile medicinal products for human use' will continue or start through 2020-2025. Collaboration relies on the existing API programme with more consideration given to collaborative inspection programmes focusing on mapping of "super sites" that require tailored and customised inspection strategies.
- A lessons learned exercise from the valsartan case, conducted by the European Medicines Network is currently underway and expected to report with recommendations for enhancement of supply chain controls by authorities and MAH's.
- New regulatory standards underpinning the evolution and implementation of novel manufacturing technologies in the globalised environment in ICH Guidelines such as Q8, Q9, Q11 and Q12. Collectively these guidelines can provide the basis for the holistic approach of enabling "lab to patient" or even "patient to patient" value chains controlled by the ICH Q10 Pharmaceutical Quality System/PQS.
  - A revision of ICH Q9 is currently planned and the provision of extensive training materials is envisaged "(with examples) that address the sources of subjectivity and uncertainty in risk assessment, as well as the role of knowledge and the need for consistency"[2].
  - A new ICH guideline, ICH Q13 'Continuous Manufacturing Of Drug Substances And Drug Products' is intended to provide harmonisation on technical and regulatory aspects unique to CM of drug substances and drug products for small and large molecules.
- Collaboration on sectoral initiatives (e.g. antibiotics, vaccines, radiopharmaceuticals) with the HMA/EMA Taskforce on availability of authorised medicines should assist through collaboration with sectoral initiatives, at national and EU level aimed at improving continuity of supply.
- A conference on improving EU manufacturing of vaccines and ensuring continuity of supply is planned to take place in 2020 co-hosted by EMA and the European Commission.
- The work of the EU-Innovation Network (EU-IN), in liaison with other HMA/EMA working groups.
- Other initiatives, e.g. One-Voice-of-Quality (https://journal.pda.org/content/73/5/517)

3.6. Sustainability of the Network and operational excellence

Strategic goals

Based on its environmental analysis of the strategic area and the identified challenges, the Network has laid down five main goals to be achieved within the strategy period:

1)	**Reinforce scientific and regulatory capacity and capability of the network**
2)	**Strive for operational excellence, building on the work done in the current strategy**

[2] ICH Q9 Draft New topic proposal

3) **Achieve a sustainable financial and governance model for the network**

4) **Develop a digital strategy to drive digital business transformation**

5) **Enable quick, consistent and adequate response to public and animal health challenges**

Recommended high-level objectives to support these goals are given in the table in Annex 1.

Sustainability of the Network and its competent authorities is key to its continued role in safeguarding public and animal health in the EU. This has to be ensured by adequate resources (financial, expertise, competence, and skills), business processes, IT capabilities, and an efficient governance structure supporting operational excellence.

The Network needs to ensure a framework for continuous optimisation that creates the right environment for change and improvement now and in the future, not only supporting better public health but allowing a vigorous and innovative European research sector to play a full part. For the Network to grow and retain its role as a major, globally-relevant regulator it must take account of an expected greater focus on integrating sustainability priorities into EU budgets and metrics, the effects of new science and new technology, as well as the challenges of new legislation and the need to manage scarce resources (ensuring an appropriate funding model and recruitment, retention and development of staff with the right competencies) supported by modern IT capabilities focused on digital transformation through simplification of processes and interfaces (see section 3.2.).

Areas that will need consideration during the strategy period include pharmaceutical policy and regulatory optimisation, financial sustainability and adequate resourcing, issues of trust and communication, IT governance and the legal and legislative frameworks within which the Network operates.

Adequate **pharmaceutical policy design** in line with the Pharmaceutical Strategy for Europe is needed to facilitate availability and the continuous supply of medicines in all EU member states, safeguard the production of sufficient active product ingredients in Europe and break existing silos between medicines and medical devices. It should also strengthen the relevance and consistency of product information for off-patent medicines. It must be combined with **regulatory optimisation** to ensure best use of scarce resources, capacity, expertise and IT capabilities - this includes approaches to work sharing (including ensuring all NCAs contribute to Network operations, for example in multinational assessment teams), data standardisation and avoiding duplication of work as well as ensuring timely availability of the right expertise and competencies within the Network (see also 3.3. above). Combining and enriching EMRN internal data with external data sources (logistics information, consumption data, e-prescription data, distribution data) will provide new opportunities for decision makers and will improve business decisions.

The network should address reduction of regulatory burden for both regulatory authorities and for our stakeholders whilst anticipating the consequences of innovation in development of new medicines and meeting stakeholders expectations with regard to off-patent medicines. The HMA/EMA Regulatory Optimisation Group is the primary platform to develop Network thinking on reduction of regulatory burden.

However, optimisation alone is not enough to ensure adequate resourcing, and thus, ultimately, the financial sustainability of the Network. To ensure adequate resourcing of all regulatory activities a proper new fee regulation safeguarding sufficient resources for the regulatory operation of the Network will be key.

The Network's outputs must meet stakeholder expectations if we are to retain and **build trust** and ensure stakeholder and wider public support for our mission. These are not solely confined to the medicines we license and whose safety we monitor, but include at their heart continuous, risk-based **communication** about our role and performance. The perceived relevance, availability, transparency, consistency and quality of the information we supply will continue to be crucial in ensuring trust and support. Communication and collaboration at an **international** level will also continue to be vital to ensure consistent responses and effective use of resources by regulators globally, all of whom face similar challenges.

Such communication also cannot be one-way. **Engaging** and bringing our stakeholders with us on the journey will be vital to the success of any strategy over the next five years. Mutual communication will be key, so that we can understand and incorporate their unique knowledge, and explain to them not only what we are doing, but why, in order to help them to understand how our actions will improve public health.

Throughout this Network strategy document the need for digital transformation and deployment of appropriate IT capabilities has been highlighted. Similar IT contributions can be utilized for various business needs. Dependency on IT services has constantly increased over time, and IT change management and service delivery are also a prerequisite for the sustainability and continuance of the Network. The functioning of the Network will largely depend on the ability to set up adequate and inter-operable IT services based on business needs and optimised business processes. Setting up the future IT landscape will trigger parallel business process developments. This requires appropriate, effective and transparent **governance** of IT-related initiatives. This future governance should enable joint decisions by business and IT based on the priorities, business value, resources and financial implications. This will be supported by improved management of project implementation. Effective governance requires timely involvement of all Network partners and stakeholders in order to deliver the benefits and business value. To manage and deliver the governance framework, an appropriate model for sharing costs, resources and knowledge is also required. Experience from the past has shown that additional resources are needed to fulfil the necessary tasks to ensure NCA involvement and effective portfolio management.

The key principles elaborated in the strategy can only be further developed if they are supported by a relevant **legal framework**, developed in close collaboration with the European Commission and the new Pharmaceutical Strategy for Europe so as to ensure early and structural involvement of regulatory authorities. New EU legislation often aims to reduce administrative burden, and any moves in this direction offer an opportunity to improve Network sustainability. In addition, appropriate framing of new legislation can take into account the potential for digitalisation, and thus allow for effective implementation of digital solutions. For all stakeholders to reap the benefits, however, the legislation has to be implemented in a harmonised way; close collaboration in the Network is necessary to achieve this. For future legislation, principles of risk and proportionality are important to ensure that our resources and expertise are used in the areas representing most risk in terms of public and animal health protection.

Among the lessons to be learned from the COVID-19 pandemic is the need for more EU coordination during public health emergencies to allow rapid and appropriate responses, and a sustainable and properly resourced Network is obviously central to such concerns. In future crises, ensuring timely approvals of relevant clinical trials and diagnostics, shortage and supply management, and providing a strong and coherent voice both within and beyond the EU will rely on a smoothly functioning and well-coordinated Network, and strengthened access to expertise and scientific leadership, as well as efficient channels of communication and clear delineation of responsibilities between the Network and other relevant stakeholders.

Challenges

- An expected greater focus on **integrating sustainability priorities** into EU budgets and metrics will need to be taken into account in Network planning and may affect **resource allocation**
- the effects of new science and new technology, as outlined in sections 3.2. and 3.3. in particular, and the need for the requisite expertise and tools to handle them, including the need for suitable IT/telematics capabilities in an environment. It may be impossible to provide a 'one-size-fits-all' model, and the Network may need to consider the possibility of its members moving at different speeds when it comes to IT development and connection.
- The challenge of **implementing the veterinary and clinical trial regulations** in a consistent and successful way
- the **need to ensure an appropriate funding model** for the Network going forward and support recruitment, retention and development of **staff with the right competencies**
- **maintaining and increasing public trust and stakeholder engagement** and addressing any concerns that changes to the regulatory system will reduce protection from unsafe or ineffective medicines
- ensuring **data consistency** across the Network for medicines and other relevant data elements and developing the reputation of the Network as a **reference source for trusted data**
- ensuring adequate **funding and resources for shared IT initiatives** and agreeing **prioritisation** where IT initiatives compete
- **addressing the gap** of funding, resources and necessary knowledge and expertise opened by non-legally driven requirements:
  - legislative requirements (SPOR [ISO IDMP], veterinary medicines regulation and CTIS) are progressing but funding and resources remain a challenge
  - non-legislative requirements (ePI, DARWIN, EU shortages database) must be considered alongside appropriate funding mechanisms, governance and prioritisation to have any chance of delivery
- the need for mechanisms to ensure **better access** to, and **wider sharing** of, existing data and decisions in order to achieve more consistent regulatory output

Interdependencies

- New fee regulation under evaluation by the European Commission
- The veterinary medicines regulation, Regulation (EU) 2019/6
- The clinical trial regulation, Regulation (EU) 536/2014
- A new EU Telematics implementation roadmap., 2021-2025
- Updated EMA 5-year framework strategy for communication and stakeholder engagement (to be finalised in 2020)

Ensuring the sustainability of the Network of course underpins all the other parts of the strategy, since without a sustainable Network the remaining themes cannot be properly addressed. However, those themes also impinge on sustainability in return, and in particular the areas of digital transformation (3.2.), and innovation (3.3.) will play a major part in determining the resources available and how they can be deployed.

4. Conclusion – putting it into practice

Following its approval by the Management Board of EMA and by the HMA, the strategy will need to be put into practice.

This document is not an explanation of every detail of the work that will be undertaken in the next 5 years. Instead it provides an overarching structure and direction, and identifies the areas which that work will need to take into account and objectives it will need to aim at. In addition, there will be a need to align with the Pharmaceutical Strategy for Europe and any future initiatives that may arise from it.

The details will be elaborated in specific work plans for EMA and HMA, which will feed into the day to day work of each component of the network. In the interests of transparency, details of workplans and programmes, and annual reports detailing activities are published by EMA on its website, and similarly, annual reports and information on work programmes are available for HMA. Information on work carried out by the NCAs at national level may also be available from their websites.

In addition to the checkpoints built into workplans and individual project planning, overall implementation of the strategy will be monitored annually, and after 18 months the Network will carry out a review, to see if the goals and objectives remain appropriate and to adjust them if necessary in the light of the changing environment.

> The need for the strategy to remain a living document, and to adjust it as the environment changes, is particularly pertinent given that its drafting has taken place while the COVID-19 pandemic was unfolding, and although the pandemic's early lessons have been taken into account as far as possible, there will undoubtedly be more to learn. Further 'lessons-learned' exercises on pandemic responsiveness are therefore anticipated within the timeframe of this strategy and will be taken into account in strategic planning

During implementation it will be essential to ensure that common or shared issues identified in development of the strategy are addressed concomitantly, to provide the most efficient and synergistic solutions and avoid the waste of resources created by silo working.

In developing its strategy the Network has been very mindful of the need to collaborate globally with bodies such as other regulators, industry associations, and international bodies and forums such as ICH. As elements of the strategy come into practice it is expected in turn that these will influence international standards like IDMP and ISO, and help in developing agreed best practice globally.

Annex 1: Objectives by focus area

The following tables provide proposals for high-level objectives to support and achieve the goals defined for each strategic focus area. Each is related to the relevant goal number for its area. These objectives will then be made concrete through specific actions to be developed and implemented in the multi-annual work plans of the Network.

Availability and accessibility of medicines

(for definition of the goals see section 3.1)

Goal	Objectives
Strengthen the availability of medicines to protect the health of European citizens and animals	Identify the specific root causes of shortages and develop strategies to improve prevention and management of shortages. A better understanding of the specific causes for shortages of generics/off-patent products versus products still under patent protection is essential.
	Help to identify and suggest areas where changes to EU or national legislation could improve supply (such as legal obligations of MAHs to maintain EU stock levels, implementation of ePI, a tool to track shortages, transparency of the supply chain and transparency of stock levels).
	Promote the availability and support uptake of biosimilars in healthcare systems
	Improve coordination of information and actions, including implementation of best practices, both for EU regulatory authorities, stakeholders and international partners
	Ensure availability of critical medicines in the EU/EEA by supporting increase of production capacity to meet demand.
	Increase transparency on availability/launch to facilitate targeted regulatory actions and communication with patients, HC professionals and HTA bodies.
Optimise the path from development, evaluation	Develop better scientific evidence which serves different decision makers along the decision chain (regulators, HTA bodies, payers)

through to access for innovative and beneficial medicines through collaboration between medicines regulators and other decision makers	Better scientific evidence to support post-licensing follow-up of medicinal products
	Stimulate the life-cycle approach to evidence generation and the possibility to adjust decisions based on new evidence
	Clear and enhanced communication to patients, health care professionals as well as down-stream decision makers about the regulatory assessment including information gap inherent for medicinal products approved on the basis of limited scientific data and secondary endpoints (eg. orphans)
	New metrics for accessibility of medicines that better represents real patient access to newly authorised medicinal products in different markets
	Foster alignment of national implementation of compassionate use programmes in order to promote equity in access for patients during late stage development and improved utilisation of data from such programmes to support later decision making

Data analytics, digital tools and digital transformation

(for definition of the goals, see section 3.2)

Goal	Objectives
Enable access to and analysis of routine healthcare data and promote standardisation of targeted data	Deliver a sustainable platform to access and analyse healthcare data from across the EU
	Enable data discoverability
	Collaborate with international initiatives on Big Data
	Establish EU framework for data quality and representativeness
Build sustainable capability and capacity within the Network	Develop EU Network skills in Big Data
	Strengthen EU Network processes for Big Data submissions

	Build EU Network capability to analyse Big Data
	Digital Transformation of the EU Network's scientific and regulatory processes to enable use of digital tool and analytics and creation of a supporting digital infrastructure – e.g. to support uptake and review of big data (from eHR, registries, devices, etc.)
Promote dynamic regulation and policy learning within the current regulatory framework	Modernise the delivery of scientific advice at central and national level
Ensure that data security and ethical considerations are embedded in the governance of data within the Network	Ensure data are managed and analysed within a secure and ethical governance framework
Map the use and needs of data analytics for veterinary medicines	Explore the use of data analytics for veterinary medicines

Innovation

(for definition of the goals, see section 3.3)

Goal	Objectives
Catalyse the integration of science and technology in medicines development and ensure sufficient network competences	Support developments in precision medicine, biomarkers and 'omics and translation of advanced therapy medicinal products (ATMPs) into patient treatments
	Transform the regulatory framework for innovative veterinary medicines through implementation of veterinary medicines regulation
	Implement an EU-level model for efficient, timely and coordinated horizon scanning and priority setting that fulfils the needs of both regulators, HTA-bodies and payers
	Enhance convergence of national decisions on classification of innovations

	Promote and invest in the PRIME scheme
	Facilitate the implementation of novel manufacturing technologies
	Foster simultaneous national scientific advice (SNSA)
	Improve expertise to accommodate rapid evolution of the regulatory system
Foster collaborative evidence generation, improving the scientific quality of evaluations and ensuring generation of evidence useful to all actors in the lifecycle of medicines	Foster innovation in clinical trials
	Leverage non-clinical models and 3Rs principles and optimise capabilities in modelling, simulation and extrapolation
	Implement the training curriculum to be developed on regulatory aspects of clinical trials within the STARS project nationally for academic centers and funding bodies
	Develop the regulatory framework for emerging clinical data generation
	Invest in special populations initiatives
	Update Environmental Risk Assessments in line with the latest scientific knowledge, make ERAs public
	Apply the latest scientific principles to the assessment of the safety of residues of veterinary medicines
	Develop further the collaboration of various groups involved with scientific advice and/or regulatory guidance
Enable and leverage research and innovation in regulatory science	Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance
Enhance collaboration with medical device experts, notified bodies and academic groups	Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science
	Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions
	Increase collaboration with Medical Device Authorities
	Identify and enable access to the best expertise across Europe and internationally

	Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders
	Promotion of early interaction with academia

Antimicrobial resistance and other emerging health threats

(for definition of the goals, see section 3.4)

Goal	Objectives
Provide high quality information on antimicrobial consumption and surveillance data on antimicrobial resistance	Adapt sales data reporting to new legislative requirements for veterinary medicine
	Adapt use data reporting to new legislative requirements for veterinary medicine
	Establish contributions to JIACRA under CVMP guidance
	Foster more robust surveillance system in the EU for both antibacterial agents consumption and emergence of resistance in human medicine
	Spread knowledge and ensure better access to data on AMR, sales and use of antimicrobials both in human and veterinary areas in line with NVR requirements
	Foster research on better understanding of causality between use of antimicrobials and AMR and of co-selection of AMR by use of biocides and feed additives
Contribute to responsible use of antibacterial agents and effective regulatory antimicrobial stewardship	Modernise S(m)PC of old antibiotics for human and veterinary use
	Define a roadmap for Point Of Care (POC) diagnostics
	Continuously raise awareness through education, best practices sharing and training
	Preserve existing therapeutic options
	Support the development of improved diagnostic test analyses requiring less time, in human and veterinary medicines

Ensure regulatory tools are available that guarantee therapeutic options while minimising impact of antimicrobial resistance on public health and the environment	Adapt existing guidelines and develop new guidance on antimicrobials (particularly taking into consideration the situation concerning limited markets in veterinary medicines) to implement new legal requirements and emerging science
	Guide clinical decision making in veterinary use of antimicrobials
	Finalise the Agency approach to antimicrobial resistance in the environment
Define pull incentives for new and old antibacterial agents	Define value of new antibacterial agents to inform new business models
	Cooperation on new business models
	Explore incentives for continuous manufacturing of old antibiotics
	Contribute to global antibiotic innovation
Foster dialogue with developers of new antibacterial agents and alternatives to traditional antimicrobials	Foster development of new antimicrobials including new antibacterials
	Define regulatory pathways for phages and other innovative products
	Reduce uncertainty for potential developers of alternatives to antimicrobials in veterinary medicines
	Engage with relevant human and veterinary stakeholders to effectively discuss the issue
	Ensuring necessary guidance is in place for authorisation of veterinary and human alternatives to antimicrobials
	Foster development of new antimicrobials for human use
Improve regulatory preparedness for emerging health threats	Refine regulatory activities in inter-epidemics periods to increase preparedness
	Harmonise regulatory framework and approaches for investigation of medicinal products during emergencies

Supply chain challenges

(for definition of the goals, see section 3.5)

Goal	Objectives
Enhance traceability, oversight and security in the human/veterinary medicine supply chain	Share information regarding manufacturers, distributors, products and respective compliance
	Tackle falsified medicines; prevent presence of falsified medicines in the supply chain
	Increase supervision of sites that produce medicinal products for a significant number of EEA markets or very significant numbers of products. . Organise a dedicated cooperative supervision between MS and strategic partners of these sites.
	Ensure adequate preparedness of new suppliers located in low- and middle-income countries on quality and production matters
Enhance inspector capacity building at EU and international level	Enhance capacity building of EU inspectors and assessors in inspections to address the problem of APIs, new technologies and continuous manufacturing
	Promote a more tailored supervision of API manufacturers through assessment and inspection of their API development and risk management practices in technology transfer
	Harmonise approach to regulatory/inspection procedures
Reinforce the responsibility for product quality by harmonising and reinforcing guidance	Develop EU level data integrity guidance
	Strengthen local supervisory authorities' understanding of EU GMP requirements
	Improving the understanding of EU GMP requirements by the manufacturers
	Ensure a level playing field and a stable EU-GMP regulatory environment with predictable outcomes
Encourage supply chain resilience and review long-term	Enhance the reliability of evidence available to regulators for informing the decision making process on the API authorization

risks resulting from dependency on limited number of manufacturers and sites	Encouraging supply chain resilience
	Promote reliability of the source of starting materials
Analyse the possible implications of new manufacturing technologies in order to regulate the new supply chains needed	Analyse the regulatory system with respect to new technologies
	Analyse the possible impacts of new technologies on the supply chain
	Identify opportunities and challenges for new technologies to improve the resilience of the supply chain
	Identify opportunities for leveraging the potential of new tools to expand the supply chain control and management

Sustainability of the Network and operational excellence

(for definition of the goals, see section 3.6)

Goal	Objectives
Reinforce scientific and regulatory capacity and capability of the network	Integrate EMA's Regulatory Science Strategy to 2025 within the EMRN 2025 Strategy
	Ensure 'fit-for-purpose' scientific capability of the Network
	Ensure optimal organisation of the available expertise within the Network
Strive for operational excellence, building on the work done in the current strategy	Optimise the current regulatory framework by ensuring efficiency of the existing regulatory operations
	Prepare for and implement the veterinary medicines Regulation
	Continue already initiated IT process improvements to further professionalise securing, provisioning and running of technology services
	Expand benefit-risk assessment and communication for human and veterinary medicines
Achieve a sustainable financial and governance model for the network	Contribute to the revision of the current fee regulation, and implement the final solution
	Ensure best use of resources through promoting mutual reliance and work-sharing
	Continuously seek effectiveness and efficiency gains to maximise use of scarce resources

Develop a digital strategy to drive digital business transformation	Establish an IT operating model and services, in support of the digital strategy and digital business transformation
Enable quick, consistent and adequate response to public and animal health challenges	Review learnings from COVID19 and strengthen EU coordination and response to public health emergencies, including crisis communication
	Build further capacity and capability within the network to support crisis management

Annex 2: Glossary

3Rs	Principles relating to the use of animals in medicines testing (Refine testing to reduce the harm to the animal, Reduce the numbers of animals required, Replace animal testing wherever and whenever it is possible)
AI	Artificial intelligence
AMR	Antimicrobial resistance
AMU	Antimicrobial use
API	Active pharmaceutical ingredient
Article 57 database	Database of authorised human medicinal products in the EU, maintained by EMA. Marketing authorisation holders are required to submit information on their medicines to the Article 57 database in accordance with Article 57(2) of Regulation (EC) No. 726/2004
ATMP	Advanced therapy medicinal product
Big Data	extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analysed computationally to reveal patterns, trends, and associations. In general, big data sets require advanced or specialised methods to provide an answer within reliable constraints
CHMP	EMA's Committee for Medicinal Products for Human Use
CMA	Conditional marketing authorisation
Co-selection	Selection of genes for resistance to an antibiotic by exposure to another substance (e.g. a different antibiotic, a heavy metal, feed additive or biocide) because the gene for resistance to the second substance is on the same shared plasmid
COVID-19	A novel coronavirus infection, first noted to affect humans in China in 2019
CTIS	Clinical Trial Information System
CVMP	EMA's Committee for Medicinal Products for Veterinary Use
DARWIN	Data Analysis and Real World Interrogation Network, a proposed EU platform to access and analyse healthcare data from across the European Union
Digital Single Market	A strategy of the European Commission to ensure the best possible access to the online world for individuals and businesses
EC	European Commission
ECDC	The European Centre for Disease Prevention and Control
EEA	The European Economic Area, comprising the EU Member States, Iceland, Liechtenstein and Norway
EFSA	European Food Safety Authority

EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network, the Network
EMVS	The European Medicines Verification System, a system for tackling falsified medicines by supplying unique identifiers that allow verification at all stages of distribution and use
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePI	Electronic product information
ERA	Environmental risk assessment
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption, a project which collects information on how antimicrobial medicines are used in animals across the European Union (EU)
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing, an EU Committee to harmonize antimicrobial breakpoints
EudraGDMP	An EU database of GMP and GDP information
EU-Innovation Network, EU-IN	A collaboration between the EU NCAs and EMA, aimed at fostering medicine innovation and early development of new medicines
EUnetHTA	European Network for Health Technology Assessment, a collaboration between HTA bodies across Europe.
EU-NTC	EU Network Training Centre, a centralised resource for training and sharing best practice in the EMRN
EU-PAS	The European Union electronic Register of Post-Authorisation Studies, a publicly available register of non-interventional post-authorisation studies maintained by EMA and hosted by ENCePP
FAIR	Guiding principles for data management and stewardship, that data should be Findable, Accessible, Interoperable and Reusable
FP	Finished product
GDP	Good distribution practice
GDPR	General Data Protection Regulation
GMO	Genetically modified organism
GMP	Good manufacturing practice
HMA	Heads of Medicines Agencies, a strategic and coordinating body representing the national medicines regulators of the EEA countries
Horizon Europe	The EU's proposed future research and innovation programme
Horizon scanning	Systematic examination of information to identify potential threats, risks, emerging issues and opportunities

HS	Horizon scanning
HTA	Health Technology Assessment (body)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IDMP	Identification of Medicinal Products, a suite of standards developed by ISO
IMI	Innovative Medicines Initiative, a public-private partnership funding health research and innovation in the EU
IRIS	EMA's online Regulatory and Scientific Information Management Platform
ISO	International Organization for Standardization
ITIL	Information Technology Infrastructure Library, a set of practices for IT service management that focuses on aligning IT services with the needs of business
ITF	Innovation Task Force (EMA)
JIACRA	Joint Inter-agency Antimicrobial Consumption and Resistance Analyses, joint reports of EMA, EFSA and ECDC that analyse data from humans and food-producing animals to better understand the occurrence of antimicrobial resistance across Europe
MAH	Marketing authorisation holder
MERS	Middle-Eastern Respiratory Syndrome, a coronavirus infection
MNAT	Multinational assessment team, a worksharing arrangement in which experts from several EU/EEA countries contribute to a medicine's assessment
MRA	Mutual recognition agreement
NCA	National competent authority, one of the national medicines regulators that form part of the Network
NITAG	National Immunization Technical Advisory Group
OECD	Organisation for Economic Co-operation and Development
One Health	an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes.
P&R	Pricing and reimbursement
payers	Authorities responsible for P&R decisions at national level
PCWP/HCPWP	EMA's Patients and Consumers Working Party and Health Care Professionals Working Party

Pharma 4.0	Use of data analytics to optimise use of resources (people, physical systems, and data) in the pharmaceutical industry
PK/PD	Pharmacokinetics and pharmacodynamics
Platform technology	a structure or technology from which various products can emerge without introducing a new process, through recombining different components or functions in various ways
PLEG	Post-launch (post-licensing) evidence generation
POC	Point-of-care (diagnostics)
Post-licensing evidence	Evidence on the efficacy and safety of a medicine produced after regulatory approval and marketing
Precision medicine	An approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle in selecting treatments
PRIME	Priority Medicines Scheme (EMA)
PSI	Public Sector Information (Directive)
Regulatory science	the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine
RWD	Real-world data
SAFe	Scaled Agile Framework, a set of workflow patterns and organisational principles for software development
SARS	Severe Acute Respiratory Syndrome, a coronavirus infection
SAWP	The Scientific Advice Working Party of EMA's CHMP
SDG	Sustainable Development Goal
SmPC	Summary of Product Characteristics, approved EU product information for healthcare professionals
SNSA	Simultaneous National Scientific Advice (pilot project of the EU Innovation Network)
SPOR	Substance, Product, Organisation and Referential master data, areas of standardised nomenclature to identify medicinal products, as developed by the ISO
STAMP	Expert Group on Safe and Timely Access to Medicines for Patients, a group providing the European Commission with advice and expertise on the implementation of EU pharmaceutical legislation, programmes and policies
STARS	Strengthening Training of Academia in Regulatory Sciences, a project of the European Commission
TATFAR	Transatlantic Task Force on Antimicrobial Resistance

Telematics	The branch of information technology which deals with the long-distance transmission of computerised information
TF	Task force
TISP	Topic Identification, Selection and Prioritisation, part of a collaborative horizon scanning project between EUNetHTA and EMA
TFAMR	Task Force on Antimicrobial Resistance of the Codex Alimentarius
VETCAST	EUCAST Veterinary Subcommittee
WHO	World Health Organization