



# Contents

|                                                                                                              |           |
|--------------------------------------------------------------------------------------------------------------|-----------|
| <b>Foreword by Prof. Guido Rasi, EMA Executive Director</b>                                                  | <b>1</b>  |
| <b>Vision — Human medicines</b>                                                                              | <b>2</b>  |
| <b>Vision — Veterinary medicines</b>                                                                         | <b>4</b>  |
| <b>1. Introduction — the regulatory framework</b>                                                            | <b>6</b>  |
| <b>2. A strategic reflection</b>                                                                             | <b>7</b>  |
| <b>3. Human medicines — five strategic goals for regulatory science</b>                                      | <b>10</b> |
| 3.1 Goal 1: Catalysing the integration of science and technology<br>in medicines development                 | 10        |
| 3.2 Goal 2: Driving collaborative evidence generation improving the scientific<br>quality of evaluations     | 19        |
| 3.3 Goal 3: Advancing patient-centred access to medicines in partnership<br>with healthcare systems          | 30        |
| 3.4 Goal 4: Addressing emerging health threats and availability/therapeutic challenges                       | 40        |
| 3.5 Goal 5: Enabling and leveraging research and innovation in regulatory science                            | 46        |
| <b>4. Veterinary medicines — four strategic goals for regulatory science</b>                                 | <b>52</b> |
| 4.1 Goal 1: Catalysing the integration of science and technology<br>in medicines development                 | 52        |
| 4.2 Goal 2: Driving collaborative evidence generation and improving the scientific quality of<br>evaluations | 57        |
| 4.3 Goal 3: Addressing emerging health threats and availability/therapeutic challenges                       | 65        |
| 4.4 Goal 4: Enabling and leveraging research and innovation in regulatory science                            | 70        |
| <b>5. Working together: international regulatory science cooperation</b>                                     | <b>75</b> |
| <b>6. List of acronyms</b>                                                                                   | <b>76</b> |

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## Foreword by Prof. Guido Rasi, EMA Executive Director

EMA's motto is "Science, Medicines, Health", meaning that science is at the foundation of everything that we do in trying to make medicines accessible to patients and animals for the benefit of public health.

The pace of innovation has accelerated dramatically in recent years and regulators need to be ready to support the development of increasingly complex medicines that more and more deliver healthcare solutions by converging different technologies to promote and protect human and animal health.

From a global perspective as I have been travelling around there is great interest expressed in horizon scanning activities to identify key innovations in science and technology that are likely to impact regulatory systems.

It is our duty to constantly challenge our capacity to regulate:

- ▶ How ready are we to engage with emerging science and technological innovations such as big data, precision medicine, novel manufacturing, novel clinical trials design, and the revolution in synthetic biology?
- ▶ Do we have the necessary skills and competencies, or indeed access to the specific expertise required?
- ▶ Are we generating new guidance or providing sufficient levels of advice to facilitate the utilisation and translation of these innovations?

This is why I asked the Chairs of the Scientific Committees to reflect upon these questions and propose our future regulatory science strategy, which was built by consulting our key stakeholders via a public consultation and workshops.

While we must absorb the disruption resulting from Brexit, the European network needs to prepare for the broader challenges that will face us as a system over the next 5 to 10 years. There are many areas where there is a need for more collaboration across the European regulatory landscape to improve the innovation environment and enhance patient access to new medicines ("more Europe in healthcare"). With regards to the veterinary landscape we have the immediate challenge of implementing the Veterinary Medicines Regulation (EU) 2019/6 over the coming years. However, we also must look beyond the Veterinary Medicines Regulation (EU) 2019/6 and attempt to engage with the challenges and opportunities presented by new technologies and their translation into veterinary medicines development.

The outcome of this exercise is a key element within the next European Regulatory Network Strategy to 2025, which will be developed together with the Member States, the European Commission and our stakeholders. It will enable us to keep on top of developments, identify the gaps between science and healthcare systems and bring together the various stakeholders needed to bridge those gaps.

# Vision — Human medicines

“To underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and innovation to be translated into patient access to medicines in evolving healthcare systems.”

## Strategic goals and core recommendations - Human medicines<sup>1</sup>

### 1. Catalysing the integration of science and technology in medicines' development

- ▶ **Support developments in precision medicine, biomarkers and 'omics**
- ▶ **Support translation of advanced therapy medicinal products (ATMPs) into patient treatments**
- ▶ Promote and invest in the PRIME scheme
- ▶ Facilitate the implementation of novel manufacturing technologies
- ▶ **Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products**
- ▶ Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals
- ▶ **Diversify and integrate the provision of regulatory advice along the development continuum**

### 2. Driving collaborative evidence generation – improving the scientific quality of evaluations

- ▶ Leverage non-clinical models and 3Rs principles<sup>‡</sup>
- ▶ **Foster innovation in clinical trials**
- ▶ **Develop the regulatory framework for emerging clinical data generation**
- ▶ **Expand benefit-risk assessment and communication**
- ▶ Invest in special populations initiatives
- ▶ **Optimise capabilities in modelling, simulation and extrapolation**
- ▶ Exploit digital technology and artificial intelligence in decision making

<sup>1</sup> The core recommendations in bold were those prioritised by the stakeholders and subsequently discussed in the 2019 workshop.

<sup>‡</sup> Core recommendations whose underlying actions have cross relevance to human and veterinary fields.

**3. Advancing patient-centred access to medicines in partnership with healthcare systems**

- **Contribute to HTA's preparedness and downstream decision making for innovative medicines**
- **Bridge from evaluation to access through collaboration with payers**
- **Reinforce patient relevance in evidence generation**
- **Promote use of high-quality real-world data (RWD) in decision-making**
- Develop network competence and specialist collaborations to engage with big data
- Deliver improved product information in electronic format (ePI)<sup>¥</sup>
- Promote the availability and support uptake of biosimilars in healthcare systems
- Further develop external engagement and communications to promote trust and confidence in the EU regulatory system

**4. Addressing emerging health threats and availability/therapeutic challenges**

- Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches
- **Continue to support development of new antibacterial agents and their alternatives<sup>¥</sup>**
- Promote global cooperation to anticipate and address supply problems<sup>¥</sup>
- **Support innovative approaches to the development, approval and post-authorisation monitoring of vaccines**
- Support the development and implementation of a repurposing framework

**5. Enabling and leveraging research and innovation in regulatory science**

- **Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science**
- Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions
- 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



## Vision — Veterinary medicines

“To foster scientific excellence in the regulation of veterinary medicines for the benefit of animal and public health while facilitating and promoting innovation and access to novel medicinal products.”

| Strategic goals and core recommendations - Veterinary medicines <sup>2</sup>                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1. Catalysing the integration of science and technology in medicines development</b>               | <ul style="list-style-type: none"> <li>▶ <b>Transform the regulatory framework for innovative veterinary medicines</b></li> <li>▶ <b>Reinforce and further embed application of the 3Rs principles<sup>¥</sup></b></li> <li>▶ Facilitate implementation of novel manufacturing models</li> </ul>                                                                                                                                                                                                                                                                                                                                |
| <b>2. Driving collaborative evidence generation - improving the scientific quality of evaluations</b> | <ul style="list-style-type: none"> <li>▶ Update Environmental Risk Assessments in line with the latest scientific knowledge<sup>¥</sup></li> <li>▶ Apply the latest scientific principles to the assessment of the safety of residues of veterinary medicines</li> <li>▶ <b>Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance</b></li> <li>▶ Develop new and improved communication and engagement channels and methods to reach out to stakeholders</li> <li>▶ <b>Develop new approaches to improve the benefit-risk assessment of veterinary medicinal products</b></li> </ul> |
| <b>3. Addressing emerging health threats and availability/therapeutic challenges</b>                  | <ul style="list-style-type: none"> <li>▶ <b>Continue to promote the responsible use of antimicrobials and their alternatives<sup>¥</sup></b></li> <li>▶ Coordinate network activities to improve data collection on antimicrobial use in animals</li> <li>▶ Engage with stakeholders to minimise the risks of antiparasitic resistance</li> <li>▶ <b>Promote and support development of veterinary vaccines</b></li> </ul>                                                                                                                                                                                                      |
| <b>4. Enabling and leveraging research and innovation in regulatory science</b>                       | <ul style="list-style-type: none"> <li>▶ Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science</li> <li>▶ Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions</li> <li>▶ Identify and enable access to the best expertise across Europe and internationally</li> <li>▶ Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders</li> </ul>                                                                                |

<sup>2</sup> The core recommendations in bold were those prioritised by the stakeholders and subsequently discussed in the 2019 workshop.  
<sup>¥</sup> Core recommendations whose underlying actions have cross relevance to human and veterinary fields.



## 1. Introduction — the regulatory framework

The European regulatory system for medicines (the 'EU network', or EMRN) is a network of all the national medicines regulators (human and veterinary) from EEA member states, the European Medicines Agency (EMA) and the European Commission. This unique system serves a population of over 400 million people.

The ultimate role of this network is to promote and protect the health of those it serves through medicines regulation. This means ensuring that both people and animals in Europe have timely access to medicines that are safe, effective and of suitable quality, as well as the information needed to use those medicines and make informed choices about their treatment.

In addition, the EU network is responsible for providing a regulatory environment that supports innovation and the development of new and better medicines to meet human and animal health needs. To do this, they must proactively engage with and foster advances in regulatory science and work closely with all their stakeholders.

### What is regulatory science?

"Regulatory science is defined as 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. It encompasses basic and applied biomedical and social sciences and contributes to the development of regulatory standards and tools."<sup>3</sup>

As science and technology advance and bring potential new treatments and diagnostic tools, regulatory science must advance in tandem so that these can be correctly, rigorously and efficiently assessed. Examples of the transformational research that is having a significant impact on the regulatory science agenda include cell-based therapies, genomics-based diagnostics, drug-device combinations, novel clinical trial design, predictive toxicology, real-world evidence, and 'big data' and artificial intelligence.

### A public health aim

The reflection on potential areas of regulatory science engagement described in this document recognises that science, technology and information (quantity, handling, dissemination) are rapidly changing society in general, and medicinal product development in particular, and that regulators must keep up.

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<sup>3</sup> Source: EMA's road map to 2015.

It follows that the EU network must have access to the best and most up-to-date scientific data, methodologies and tools available on which to base decisions. We recognise too that regulators are only one element in the decision-making chain, and that continued and expanded collaboration with our stakeholders and partners at every level is key to ensuring that patients and animals and caregivers have the medicines they need, and the information required to make decisions about their use. The proposed goals, recommendations and actions aim to ensure that regulators can advance protection of public health and provide European citizens with optimal medicines regulation in the coming years. They will also aid the delivery of several UN [Sustainable Development Goals](#) (SDG), mainly within [SDG Goal 3](#) (3.4, 3.D).

including health technology assessors and payers, and the pharmaceutical industry. This diverse group of stakeholders all have a role to play in the ongoing development of the network.

## **Who are our stakeholders?**

Ultimately, what we do is intended for the benefit of patients and animals. They, and the healthcare professionals who treat them, are at the core of our mission. In order to serve them well, and through them wider civil society, we must also engage with the needs of academic and research communities, other regulatory and government institutions





## 2. A strategic reflection

This strategic reflection sets out working proposals on the key areas with which EMA intends to engage, in order to ensure that it has the regulatory tools to continue supporting the network and fulfilling its ongoing mission despite new scientific challenges. The document identifies 5 strategic goals for such engagement on the human medicines side, and 4 aligned strategic goals for veterinary medicines; it proposes core recommendations and underlying actions that would need to be taken to support these.

The goals and proposed recommendations in the strategic reflection have been prepared in collaboration with our many stakeholders.

### How were the goals and recommendations derived?

In its central role within the EU network, EMA and its 7 scientific committees must routinely engage with advances in regulatory science, a process planned and monitored through its multiannual work programme and coordinated by its Scientific Coordination Board (SciCoBo).

During an environmental impact assessment conducted in 2016 the need for a strategic reflection was identified. The aim was to allow best allocation of necessarily limited network resources to areas where

the impact would be greatest. This need was made even more acute as a result of the UK leaving the EU.

To begin the reflection process, SciCoBo commissioned a detailed baseline report in 2017 looking at the key trends in science, technology and regulation that will impact the operations of EMA and the network. This report built on EMA's extensive and ongoing work in many of these areas, and a developing horizon-scanning capacity.

To build in stakeholder input from the early stages, an extensive series of outreach activities were conducted with stakeholders at all levels of the medicine development pathway:

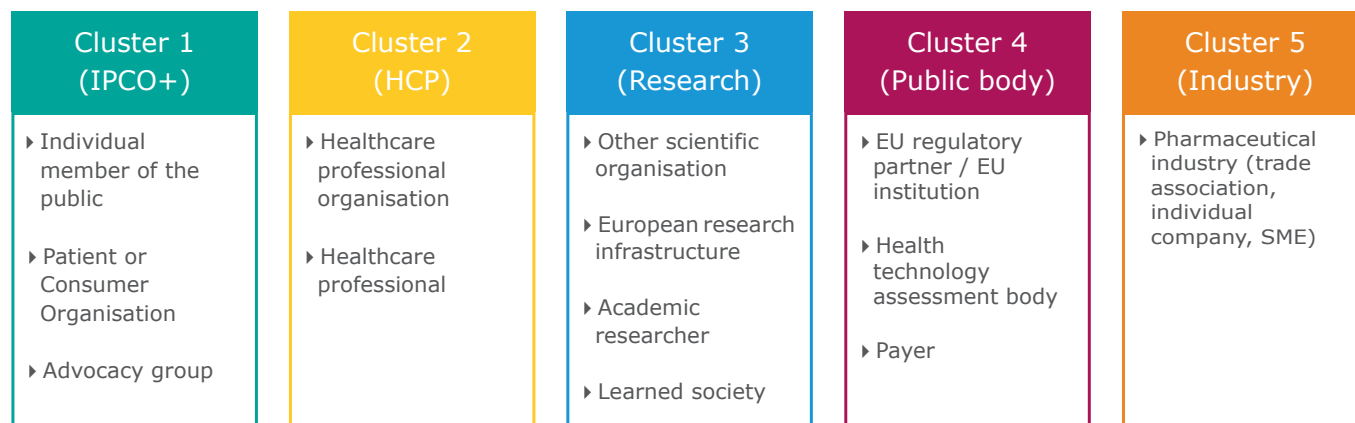
- ▶ Healthcare professionals and patient representative groups
- ▶ European research infrastructure networks, scientific organisations and associations, and academic scientists
- ▶ Experts in regulatory science (chairs of all EMA working parties and Scientific Advisory Group chairs)
- ▶ Representatives from health technology assessors and payers

- ▶ Representatives of industry, small and medium size enterprises and industry associations

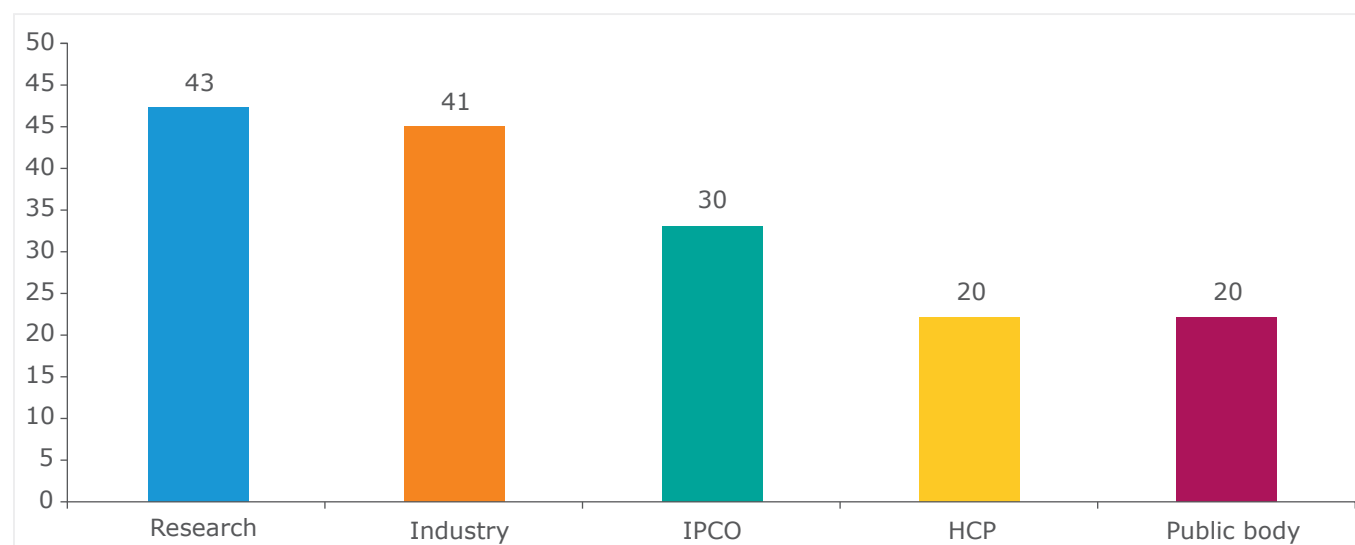
All the inputs from these exercises were distilled into this strategic reflection document, which

was presented at the end of 2018 for a 6-months public consultation to allow the wider stakeholder community to have its say. Responses received were both qualitative and quantitative.

**Figure 1.** Stakeholder types: how responses were grouped



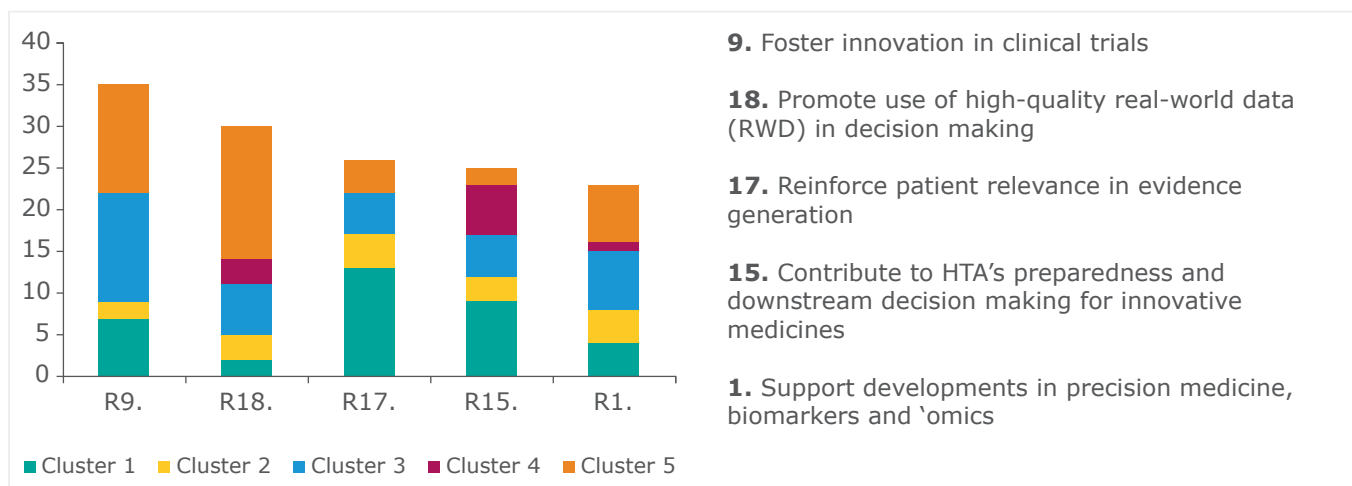
**Figure 2.** Responses to the public consultation by stakeholder type



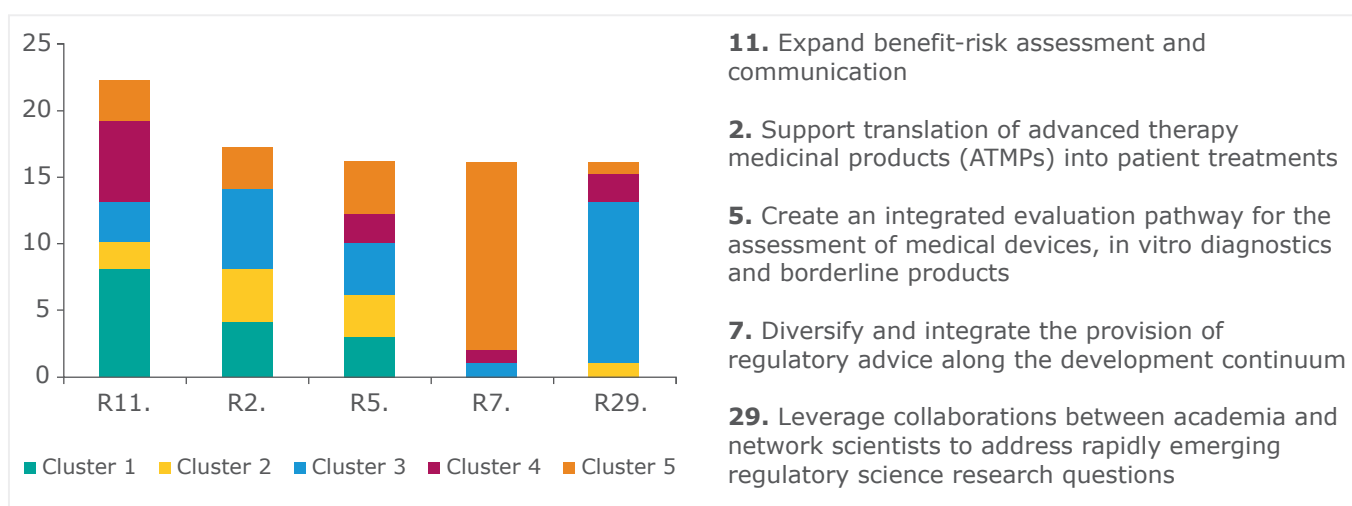
Stakeholders were asked to identify the core recommendations that they believed would deliver the most significant change in the regulatory system over the next five years.

The cumulative results by stakeholder group are presented in figures 3 and 4 for the human area and 5 and 6 for the veterinary area.

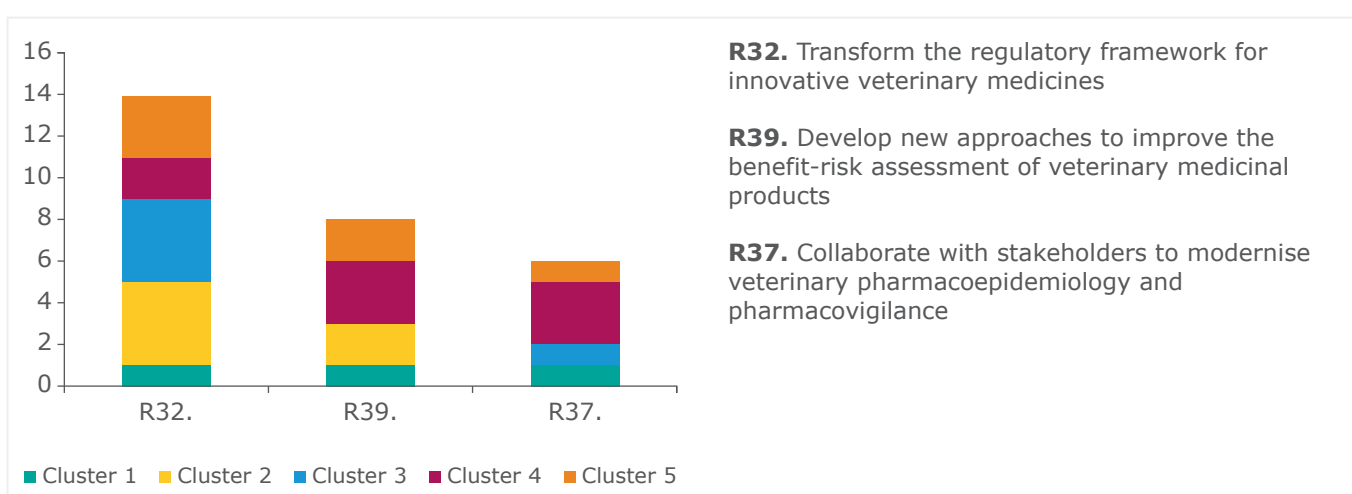
**Figure 3.** Top 5 core recommendations thought to deliver the most significant change - Human



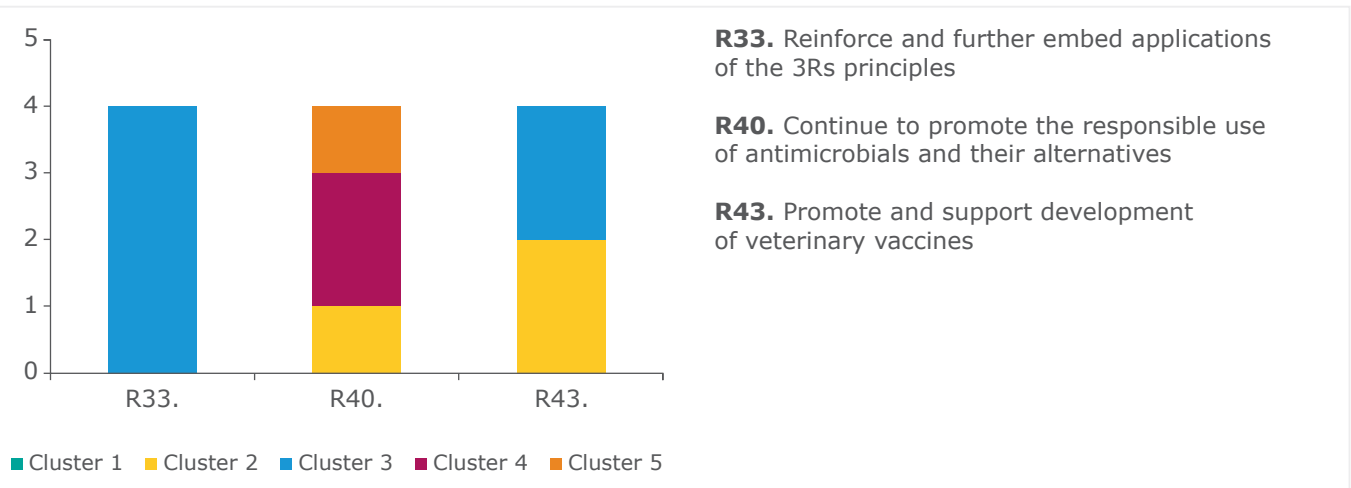
**Figure 4.** Next 5 core recommendations thought to deliver the most significant change - Human



**Figure 5.** Top 3 core recommendations thought to deliver the most significant change - Veterinary



**Figure 6.** Next 3 core recommendations thought to deliver the most significant change - Veterinary



In 2019, we used the ranking results above to hold finalisation [workshops](#) to develop the core recommendations that were expected to deliver the most significant change over the next five years.

The qualitative responses were summarised using framework analysis<sup>4</sup> and the detailed results can be found [here](#).

All comments received on the draft EMA ‘Regulatory science to 2025’ strategy can be found [here](#).

As a result of the analysis of the responses received during the public consultation and the feedback received during the workshops, we have updated the strategy to include revised core recommendations and underlying actions. The extensive responses received identified a multiplicity of actions, many of which are too detailed to be included within this strategic reflection. These will nevertheless be taken into account in the detailed implementation planning.

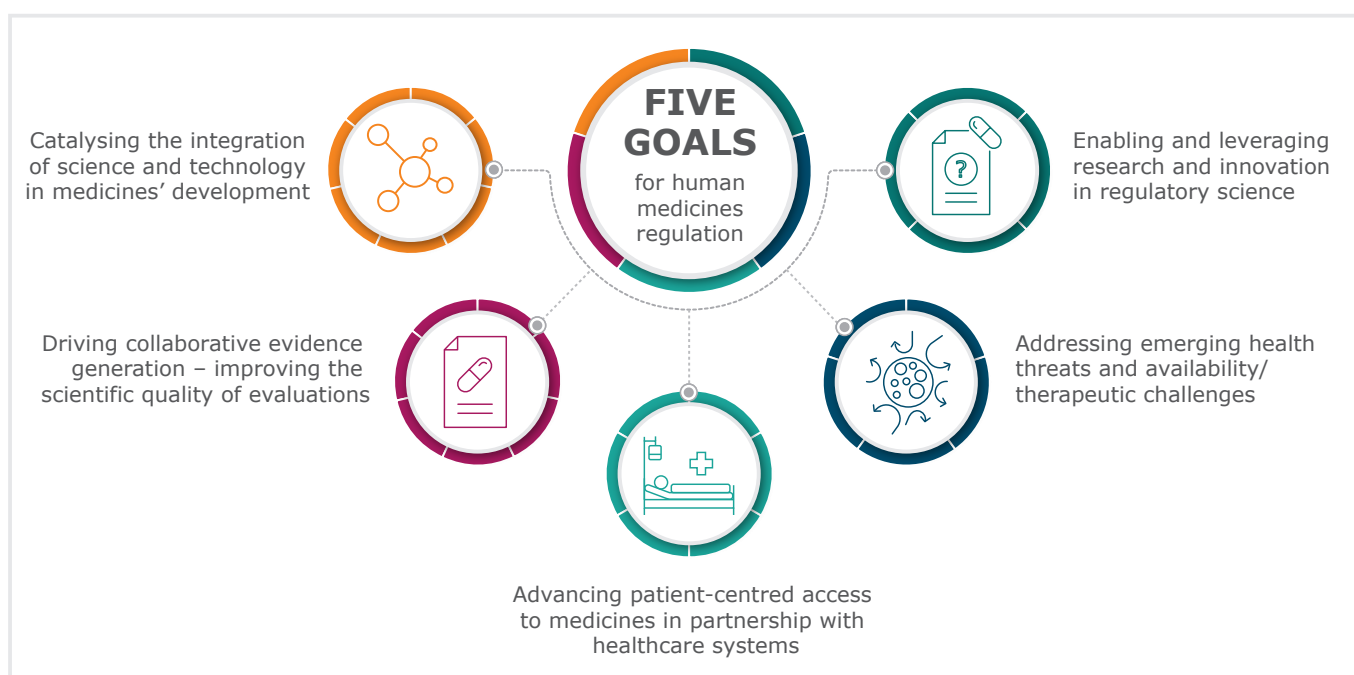
This implementation planning will establish prioritisation and measurable outcomes for each core recommendation and its underlying actions. These will be translated into detailed initiatives and embedded into work plans for EMA and its scientific committees/working parties. In addition, actions involving the network will inform the development of the network strategy for the next 5 years, and will be delivered via the HMA multiannual workplan, and the National Competent Authorities’ workplans.

4 1. Gale N, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC medical research methodology. 2013;13(1):117.  
2. Lacey A, Luff D. Qualitative Research Analysis: The NIHR RDS for the East Midlands / Yorkshire & the Humber; 2007.



### 3. Human medicines — five strategic goals for regulatory science

**Figure 7.** Human strategic goals



EMA seeks to help regulatory science develop and use it to ensure that advances in knowledge translate in a timely way into new, safe and effective treatments for patients.

The vision for human medicines is that to underpin its mission of protecting human health, EMA must catalyse and enable regulatory science and

innovation to be translated into patient access in evolving healthcare systems.

To this end, 5 strategic goals are proposed. Each is associated with a set of core recommendations and their supporting actions.



### 3.1 Goal 1: Catalysing the integration of science and technology in medicines developments

Summary table

The ultimate public health aim is to ensure that regulation can support the development of new medicines and innovative techniques, so that patients’ needs can be better addressed with safer, more effective and clinically appropriate treatments. This requires the network to address, for example, moves to more patient-centred healthcare, and precision, or personalised, medicine.

We wish to see the latest scientific and technological knowledge built into medicines development where it benefits public health. This requires closer collaboration with academics, research centres and infrastructures and ensuring that this is embedded into the ongoing dialogue between regulators and developers at all stages of the process. Such dialogue is vital to ensure that evidence generation plans are designed to address relevant questions for later decision making, so that patients are only enrolled in relevant and high-quality study programmes. Building on and developing existing mechanisms for this, in particular the scientific advice processes that already form a successful part of the EU network’s regulatory pathways, EMA is proposing the core recommendations outlined below.

| Catalysing the integration of science and technology in medicines development              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|--------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                       | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Support developments in precision medicine, biomarkers and ‘omics                          | <ul style="list-style-type: none"><li>▶ Enhance early engagement with novel biomarker developers to facilitate regulatory qualification:<ul style="list-style-type: none"><li>» Critically review the EMA’s biomarker validation process, including duration and opportunities to discuss validation strategies in advance, in order to encourage greater uptake and use;</li></ul></li><li>▶ Address the impact of emerging ‘omics’ methods and their application across the development life cycle;</li><li>▶ Evaluate, in collaboration with HTAs, payers and patients, the impact of treatment on clinical outcomes measured by biomarkers;</li><li>▶ Optimise the European research infrastructure for developing personalised medicine.</li></ul> |
| Support translation of advanced therapy medicinal products (ATMPs) into patient treatments | <ul style="list-style-type: none"><li>▶ Identify therapies that address unmet medical need;</li><li>▶ Provide assistance with early planning, method development and clinical evaluation;</li><li>▶ Address the challenges of decentralised ATMP manufacturing and delivery locations;</li><li>▶ Support evidence generation, pertinent to downstream decision-makers;</li></ul>                                                                                                                                                                                                                                                                                                                                                                        |

**Support translation of advanced therapy medicinal products (ATMPs) into patient treatments**

- ▶ Evaluate and improve interactions relevant to ATMPs with European institutions (research, financial and environmental);
- ▶ Raise global awareness of ATMPs to maximise knowledge sharing, promote data collection;
- ▶ Engage with other international regulatory agencies to foster global convergence of requirements for ATMPs.

**Promote and invest in the PRIME scheme**

- ▶ Improve external communication to better explain and promote PRIME;
- ▶ Review the scientific advice provided in PRIME with a view to allow more flexibility in the procedure and identify opportunities for more agile discussions;
- ▶ Optimise the current regulatory system that supports PRIME in order to enable a shortened time frame for development and MA review while ensuring high quality evidence generation plans to improve access for patients;
- ▶ Review the performance of the scheme after 5 years, to ensure that it delivers the expected impact on public health (i.e. faster access to patients of priority medicines), and adapt its scope and features, if applicable;
- ▶ Explore opportunities for further engagement and collaboration with patients, healthcare professionals, academia and international partners;
- ▶ Explore possible impact and benefits of expanding the earliest possible entry to the PRIME scheme to a wider range of applicants, including for new indications of existing products.

**Facilitate the implementation of novel manufacturing technologies**

- ▶ Recruit and develop expertise, in novel manufacturing technologies and develop training and tools to enhance the assessment process;
- ▶ Identify potential bottlenecks and strengthen early interaction, transparency and communication with stakeholders on regulatory requirements for novel manufacturing technologies;
- ▶ Address regulatory challenges through modernisation of relevant regulations and guidelines to facilitate novel manufacturing technologies, including through international harmonisation activities;
- ▶ Encourage the use of risk-based approaches to manufacturing processes and control strategies throughout the product lifecycle;
- ▶ Facilitate a flexible and fit for purpose approach in application of Good Manufacturing Practice;

|                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Facilitate the implementation of novel manufacturing technologies</b>                                                           | <ul style="list-style-type: none"> <li>▶ Support the development of greener manufacturing technologies in line with the EU's 'Strategic Approach to Pharmaceuticals in the Environment'.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products</b> | <ul style="list-style-type: none"> <li>▶ Facilitate the regulatory pathway between notified bodies and medicines' regulators:             <ul style="list-style-type: none"> <li>» Establish a process for multi-stakeholder scientific advice to support development of medicine-device combinations, qualification methodologies and the use of companion diagnostics;</li> <li>» Create a process to consult medical device authorities and/or notified bodies (as applicable) for device-related aspects throughout the product lifecycle, including post-authorisation safety related events;</li> <li>» Adapt consultation processes to address emerging digital technologies and wearables;</li> </ul> </li> </ul>                                           |
| <b>Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products</b> | <ul style="list-style-type: none"> <li>▶ Build a network of expertise to regulate and provide support throughout the product lifecycle;</li> <li>▶ Define how benefit-risk of borderline products is assessed and communicated;</li> <li>▶ Gain insight in innovation on drug-device combination products via horizon scanning.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals</b>                   | <ul style="list-style-type: none"> <li>▶ Raise awareness of new nanomedicines and materials via the EU-Innovation Network, and foster collaboration with DG JRC and other international partners (e.g. IPRP), to share knowledge and harmonize regulatory practices:             <ul style="list-style-type: none"> <li>» Generate guidance addressing PK/PD (including modelling) requirements and long-term efficacy and safety;</li> <li>» Develop and standardise new testing methods related to the quality and safety assessment of nanomedicines;</li> <li>» Understand the critical quality attributes (CQA) of a given product and the relationship between those and the biological activity and in-vivo behaviour of the product;</li> </ul> </li> </ul> |
| <b>Diversify and integrate the provision of regulatory advice along the development continuum</b>                                  | <ul style="list-style-type: none"> <li>▶ Create complementary and flexible advice mechanisms to support innovative product development also expanding multi-stakeholder consultation platforms;</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

**Diversify and integrate the provision of regulatory advice along the development continuum**

- ▶ Facilitate a more iterative advice framework that better addresses the continuum of evidence generation. Make general advice on new technological trends publicly available;
- ▶ Promote more integrated medicines development aligning scientific advice, clinical trials approval and Good Clinical Practice oversight;
- ▶ Advance acceptance of digital endpoints through exploring a multistakeholder platform to generate feedback on their utility;
- ▶ Facilitate translation of innovation via a re-engineered Innovation Task Force and synergy with an evolving EU-Innovation Network platform.

### 3.1.1 Support developments in precision medicine, biomarkers and 'omics

Precision or personalised medicines may range from targeted drugs aimed at stratified populations (biomarker-led medicine) or different stages of the disease, to the use of individualised treatment such as modified autologous cells. The development of biomarkers of various types, including the increasing use of 'omics'-based biomarkers, is a key enabler of precision medicine.

The early involvement of stakeholders at all levels will be key to finding solutions that allow approved biomarker-guided medicines to be made accessible to patients. Regulatory assessment will need to be further developed to deal with more complex medicines designed and manufactured for a specific individual. Continuous evidence generation and ways to handle the large volumes of data likely from new diagnostics will also need to be embedded in the regulatory process to support the entry of precision medicines into public healthcare systems.

The agency is proposing actions aiming to develop methods/guidelines for qualifying biomarkers; efficient procedures for qualification; and fostering interaction with other stakeholders.

The actions proposed by EMA to support this recommendation are:

- ▶ Enhance early engagement with novel biomarker developers to facilitate regulatory qualification:

- » Critically review the EMA's biomarker validation process, including duration and opportunities to discuss validation strategies in advance, in order to encourage greater uptake and use;

- ▶ Address the impact of emerging 'omics' methods and their application across the development life cycle;
- ▶ Evaluate, in collaboration with HTAs, payers and patients, the impact of treatment on clinical outcomes measured by biomarkers;
- ▶ Optimise the European research infrastructure for developing personalised medicine.

### 3.1.2 Support translation of advanced therapy medicinal products (ATMPs) into patient treatments

ATMPs (somatic cell therapies, tissue engineered products, gene-therapies) have great potential to address unmet medical needs and techniques such as genome editing have the potential to treat, and potentially cure, a broad range of diseases that are not adequately addressed by currently available therapies.

The number of applications for approval has been, however, very limited. This has been in part attributed to factors such as use of such products already at national level through the hospital exemption route. This creates challenges in evidence generation for these products that would benefit from a more coordinated approach across the EU network and with international partners. Other challenges facing ATMPs include the fact that early development of these products mostly

takes place in academia and SMEs which typically require additional regulatory advice, the problems of consistently manufacturing, for example, cell-based products throughout their development and use, and delivering them efficiently to the patient's bedside, and in some cases particular ethical and social concerns. Creative payment models are also needed to ensure affordability of, and access to, ATMPs.

Despite ongoing efforts in this area, more remains to be done to address both current challenges and those that will arise from emerging technological advances in the ATMP field. Thus, the Agency proposes the following actions to promote ATMP development in Europe and faster patient access to treatments:

- ▶ Identify therapies that address unmet medical need;
- ▶ Provide assistance with early planning, method development and clinical evaluation;
- ▶ Address the challenges of decentralised ATMP manufacturing and delivery locations;
- ▶ Support evidence generation, pertinent to downstream decision-makers;
- ▶ Evaluate and improve interactions relevant to ATMPs with European institutions (research, financial and environmental);
- ▶ Raise global awareness of ATMPs to maximise knowledge sharing, promote data collection;
- ▶ Engage with other international regulatory agencies to foster global convergence of requirements for ATMPs.

### **3.1.3 Promote and invest in the PRIME scheme**

The PRIME scheme was launched in March 2016 to provide early and enhanced scientific and regulatory support to medicines that have significant potential to address unmet medical needs. The scheme has been broadly successful in bringing forward proposals to speed the development and timely approval of medicines for conditions that have proved difficult, if not impossible, to treat.

In the light of the above, EMA is recommending that the scheme be refined based on experience to date. However PRIME is resource intensive, requiring regular, timely access to appropriate expertise in the regulatory system with many products also requiring extensive monitoring of post-licensing evidence generation. Involvement of HTAs is crucial, so that scientific advice takes into account their evidence requirements, facilitating decision making on reimbursement and patient access. Building on interactions with key stakeholders, including the EU-Innovation Network, to help in identifying and supporting PRIME candidates at national level, and collaboration with patients, healthcare professionals, academia and international partners such as the FDA (Breakthrough designation) and PMDA (Sakigake designation), will be needed to allow PRIME to be better understood and further developed. Further optimisation of the current regulatory system is also needed to enable timely patient access and shorten review times while ensuring pre-licensing evidence generation of sufficient quality.

The Agency therefore proposes the following categories of action:

- ▶ Improve external communication to better explain and promote PRIME;
- ▶ Review the scientific advice provided in PRIME with a view to allow more flexibility in the procedure and identify opportunities for more agile discussions;
- ▶ Optimise the current regulatory system that supports PRIME in order to enable a shortened time frame for development and MA review while ensuring high quality evidence generation plans to improve access for patients;
- ▶ Review the performance of the scheme after 5 years, to ensure that it delivers the expected impact on public health (i.e. faster access to patients of priority medicines), and adapt its scope and features, if applicable;
- ▶ Explore opportunities for further engagement and collaboration with patients, healthcare professionals, academia and international partners;



- ▶ Explore possible impact and benefits of expanding the earliest possible entry to the PRIME scheme to a wider range of applicants, including for new indications of existing products.

### 3.1.4 Facilitate the implementation of novel manufacturing technologies

Technological development is allowing new and more efficient ways of manufacturing medicines. These new manufacturing methods include, for example, continuous manufacturing, an alternative to traditional batch processing in which raw materials are continually input at one end of the process and output materials continuously collected and additive manufacturing (“3D printing”), which is intended for the production of complex customised products designed to address the needs of an individual patient, including production at the point of care, as well as processes employing innovative analytical technologies and technologies for producing advanced therapy medicinal products (ATMPs). Through innovative use of digital tools and data, these techniques offer an opportunity to reduce waste, produce medicines in more flexible and responsive ways and tailor production to specific, even individual, medical needs. Their implementation should therefore be facilitated by the regulatory system.

These new technologies may not fit exactly into the traditional regulatory models, and may necessitate adaptation or changes to GMP requirements and standards and the development of specific regulatory guidance and monitoring to support their implementation while maintaining quality. In addition, regulators will need to develop expertise to allow adequate oversight of these new processes.

The Agency is thus proposing that the system should:

- ▶ Recruit and develop expertise, in novel manufacturing technologies and develop training and tools to enhance the assessment process;
- ▶ Identify potential bottlenecks and strengthen early interaction, transparency and communication with stakeholders on regulatory requirements for novel manufacturing technologies;
- ▶ Address regulatory challenges through modernisation of relevant regulations and guidelines to facilitate novel manufacturing technologies, including through international harmonisation activities;
- ▶ Encourage the use of risk-based approaches to manufacturing processes and control strategies throughout the product lifecycle;
- ▶ Facilitate a flexible and fit for purpose approach in application of Good Manufacturing Practice;
- ▶ Support the development of greener manufacturing technologies in line with the EU’s ‘Strategic Approach to Pharmaceuticals in the Environment’.

### 3.1.5 Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products

An increasing number of complex products are emerging that combine a medicine and a medical device. Consequently, it is becoming ever more difficult to attribute one primary mode of action to the combined product; for example, to separate the contribution of biological/pharmacological or physicochemical mechanisms to the clinical benefit-risk assessment. In addition, an increasing number of innovative medicines depend on the use of an associated in-vitro diagnostic.

With the number of complex medicines expected to increase, the EU regulatory network identified the need to find new ways for collaboration with all relevant stakeholders, including notified bodies and authorities responsible for regulating medical devices. This will allow the EU network to establish a more integrated risk/benefit assessment of such products and evaluate all relevant components, while avoiding unnecessary regulatory burden. It will also support the development of innovative medicines, and better respond to changing environments, through building competence and expertise across different disciplines.

Strengthened regulatory decision making for borderline products could result in significant patient benefit and, at the same time, enhance the growth of a major health sector in Europe. While the new

EU medical device and in-vitro diagnostic regulations (MDR and IVDR) already require collaboration for certain types of medicine and device combinations, extension of this collaborative approach may be envisaged for other types of medicine-device combinations of the future.

The actions proposed by EMA to support this recommendation are:

- ▶ Facilitate the regulatory pathway between notified bodies and medicines' regulators:
  - » Establish a process for multi-stakeholder scientific advice to support development of medicine-device combinations, qualification methodologies and the use of companion diagnostics;
  - » Create a process to consult medical device authorities and/or NB (as applicable) for device-related aspects throughout the product lifecycle, including post-authorisation safety related events;
  - » Adapt consultation processes to address emerging digital technologies and wearables;
- ▶ Build a network of expertise to regulate and provide support throughout the product lifecycle;
- ▶ Define how benefit-risk of borderline products is assessed and communicated;
- ▶ Gain insight in innovation on drug-device combination products via horizon scanning.

### **3.1.6 Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals**

New 'smart' materials that interact with external stimuli to change their properties in a predictable way, and nanomedicines whose properties and characteristics derive from components at nano-scale size, are being developed for pharmaceuticals and medical devices. They offer the potential for innovative treatments and improved delivery systems for active substances, addressing an unmet medical need.

However due to their complexity they also pose a number of scientific and regulatory challenges. These may include, for example, the need for development and standardisation of new testing methods and understanding of the correlation between critical quality attributes and in-vivo behaviour.

Further, such products are particularly likely to be borderline medical devices, in which the contribution of biological/pharmacological and physicochemical mechanisms is hard to distinguish (see above).

Appropriate expertise therefore needs to be acquired, in partnership with other bodies such as those responsible for regulating medical devices, to ensure the rigorous evaluation of future products of this type.

In order to develop the necessary understanding of nanotechnology and new materials, the Agency proposes to implement the following actions:

- ▶ Raise awareness of new nanomedicines and materials via the EU-Innovation Network, and foster collaboration with DG JRC and other international partners (e.g. IPRP), to share knowledge and harmonize regulatory practices:
  - » Generate guidance addressing PK/PD (including modelling) requirements and long-term efficacy and safety;
  - » Develop and standardise new testing methods related to the quality and safety assessment of nanomedicines;
  - » Understand the critical quality attributes (CQA) of a given product and the relationship between those and the biological activity and in-vivo behaviour of the product;

### **3.1.7 Diversify and integrate the provision of regulatory advice along the development continuum**

The rate at which biomedical science and technology are changing means there is a need for more flexible and timely interaction between medicine developers and regulators – indeed, the need for earlier and more frequent dialogue to support development is a recurrent theme when the former stakeholder group are surveyed. Improving scientific advice

and expediting guidance will bring more tailored treatments for patients faster, through, for example, improving trial designs and avoiding unnecessary trials for patients while maintaining appropriate safeguards.

To optimise patient access and make the development process as efficient as possible, scientific and regulatory advice and guidance needs to be provided throughout the development and decision-making phases of a product, with the involvement of patients, healthcare professionals, HTAs and payers from the early stages.

The Agency recommends investment of the necessary resources to strengthen and improve the current scientific advice platforms so that product-driven advice can address multiple development options. To this end it proposes to:

- ▶ Create complementary and flexible advice mechanisms to support innovative product development also expanding multi-stakeholder consultation platforms;
- ▶ Facilitate a more iterative advice framework that better addresses the continuum of evidence generation. Make general advice on new technological trends publicly available;
- ▶ Promote more integrated medicines development aligning scientific advice, clinical trials approval and Good Clinical Practice oversight;
- ▶ Advance acceptance of digital endpoints through exploring a multistakeholder platform to generate feedback on their utility;
- ▶ Facilitate translation of innovation via a re-engineered Innovation Task Force and synergy with an evolving EU-Innovation Network platform.

### 3.2 Goal 2: Driving collaborative evidence generation — improving the scientific quality of evaluations

The public health aim of our second goal is to provide regulators and HTAs/payers with better evidence to underpin regulatory assessment and decision-making, so that patients can gain more timely access to beneficial treatments while continuing to be protected from medicines whose benefits do not outweigh their risks. It also aims to address the unmet medical needs of paediatric populations, rare orphan conditions and conditions of high individual and public health burden lacking satisfactory treatments.

Underlying much of this is the increasing incorporation of new digital tools into medicines manufacturing, development and clinical care protocols. This means that data could be more widely and efficiently collected throughout the lifecycle of a medicine, from preclinical development, through the clinical trial process, and into real world use. Improved evidence generation also offers a chance to capture patient preferences better during the evaluation process and make clinical development and regulation more cost-effective, potentially reducing the burden on healthcare systems.

#### Summary table

| Driving collaborative evidence generation – improving the scientific quality of evaluations |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                        | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Leverage non-clinical models and 3Rs principles                                             | <ul style="list-style-type: none"><li>▶ Stimulate developers to use novel pre-clinical models where appropriate, including those adhering to the 3Rs:<ul style="list-style-type: none"><li>» Cooperate with other EU agencies/bodies to fund research and (access to) standardised repositories for alternative methods and models;</li><li>» Development of clear guidance to encourage and prioritise the use of New Approach Methodologies (NAMs) that can be used to fulfil testing requirements in lieu of traditional animal tests and that take the 3Rs into serious consideration;</li></ul></li><li>▶ Re-focus the role of the Joint 3Rs working group (J3R WG) to support qualification of new alternative 3R-compliant methods/models including in silico and novel in vitro assays;</li><li>▶ Implement/develop IT tools to exploit the added value of SEND for the re-analyses of non-clinical studies to support clinical trials, marketing authorisation and improved evidence generation.</li></ul> |
| Foster innovation in clinical trials                                                        | <ul style="list-style-type: none"><li>▶ Establish a multi-stakeholder, neutral, platform, to enable new approaches to clinical studies and to position the EU as a preferred location for innovative clinical research;</li><li>▶ Drive development and adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance at EU and international level;</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

**Foster innovation in clinical trials**

- ▶ Work with stakeholders, the EU Medicines Regulatory Network and the European Commission to promote and facilitate the conduct of complex clinical trials and other innovative clinical trial designs;
- ▶ Promote increased information sharing on clinical trial design, conduct, results and best practices. Build on this information and the multi-stakeholder platforms to enable further education, training and sharing of best practice in order to accelerate innovative change;
- ▶ Critically assess the clinical value of new and emerging endpoints and their role in facilitating patients' access to new medicines;
- ▶ Promote the inclusion of neglected populations such as pregnant women, the elderly and those of diverse ethnicity in clinical trials.

**Develop the regulatory framework for emerging clinical data generation**

- ▶ Develop methodology to incorporate clinical care data sources in regulatory decision-making;
- ▶ Clarify questions on data ownership and data security;
- ▶ Modernise the GCP regulatory oversight to enable decentralised models of clinical trials coupled with direct digital data accrual;
- ▶ Develop the capability to assess complex datasets captured by technology such as wearables;
- ▶ Facilitate training and understanding of healthcare professionals and patients to access and participate effectively in such trials;
- ▶ Support the development of robust digital endpoints through qualification, scientific advice, and the establishment of a multi-stakeholder platform to obtain feedback on their utilisation.

**Expand benefit-risk assessment and communication**

- ▶ Include patient preferences to inform the benefit-risk assessment:
  - » Develop guidance building on recent developments (e.g., IMI PREFER) of appropriate methods for patient preference study design, conduct, analysis, and presentation for regulatory purposes, ensuring high quality methodology and independence;
  - » Provide guidance on the roles of patient preferences in the different therapeutic contexts and regulatory decisions, i.e., how preferences can help regulators interpreting clinical trial outputs, how they can inform shared decision-making; how to handle heterogenous or conflicting preferences; how to communicate patient preferences in regulatory decisions;

**Expand benefit-risk assessment and communication**

- ▶ Promote systematic application of structured benefit-risk methodology and quality assurance systems in the approach to assessment and consistency of decision-making;
- ▶ Enhance structured assessment of benefits, harms, and uncertainties to improve communication to the public;
- ▶ Develop the capability for analysing individual patient data to support decision-making;
- ▶ Improve communication with HTAs and payers regarding therapeutic context, comparison vs. placebo/active-control, patient perspective.

**Invest in special populations initiatives**

- ▶ Focus on accelerating access for patient (sub-)populations in urgent need whilst ensuring high quality data to evaluate efficacy and safety of medicines;
- ▶ Identify areas of highest unmet needs where clinical care data can supplement clinical trial data;
- ▶ Foster input of patients/patient representatives and carers in the regulatory process and enhance multi-stakeholder advice in collaboration with patients, HCPs, payers and HTAs;
- ▶ Progress implementation of the geriatric medicines strategy;
- ▶ Progress implementation of the joint EMA/EC paediatric medicines action plan:
  - » Participate in multi-stakeholder initiatives on neonatal medicines to further the understanding of disease mechanisms and natural history and develop models of disease progression to support innovative clinical trial design, biomarkers and endpoints that accurately capture treatment benefit;
- ▶ Develop a strategic initiative in maternal-foetal health with other regulators and international stakeholders, to advance access through better understanding and communication of benefits, risks, and uncertainties of medicines use in pregnancy and breastfeeding:
  - » Such an initiative should include considerations regarding PK/PD modelling, epigenetics, reproductive toxicity studies, clinical trial design as well as post-authorisation follow-up methods;
- ▶ Encourage research to improve the efficiency and effectiveness of detecting drug safety issues (signal detection) in pregnant women and the elderly.



**Optimise capabilities  
in modelling,  
simulation and  
extrapolation**

- ▶ Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects;
- ▶ Develop guidance and standards on the use of AI in modelling and simulation for regulatory submissions;
- ▶ Deploy advances in RWD, modelling, simulation and extrapolation to benefit special populations particularly neglected patient populations;
- ▶ Promote development and international harmonisation of methods and standards via a multi-stakeholder platform;
- ▶ Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange:
  - » Invest in Centres of Excellence in regulatory science at an EU level, to work with regulatory agencies to provide training and research on modelling & simulation tools;
  - » Enhance collaboration with external partners/consortia with expertise in modelling and simulation, and EU funded or co-founded projects e.g. IMI, Horizon 2020;
- ▶ Investigate possibilities for conducting modelling and simulation analyses to address key regulatory questions as part of product specific assessment or development of guidelines and policies;
- ▶ Consider working with stakeholders to foster data sharing through developing data standards and platforms for data exchange.

**Exploit digital  
technology and  
artificial intelligence in  
decision making**

- ▶ Establish a digital innovation lab to explore, pilot and develop solutions and processes, across the drug regulation spectrum, that leverage novel digital technology and artificial intelligence to support increase in efficiency and regulatory decision-making;
- ▶ Develop capacity and expertise across the regulatory network through curriculum development and knowledge-sharing initiatives on data science, digital technologies and artificial intelligence- related solutions, products and endpoints, and their applications in the regulatory system;
- ▶ Create and maintain a Health Data Science and AI forum to engage with a diverse set of stakeholders in novel digital technologies and artificial intelligence. This will include the technical, ethical, legal, regulatory and scientific perspectives of the use of digital technologies, and AI-powered applications;

### **Exploit digital technology and artificial intelligence in decision making**

- ▶ Establish a dedicated framework for the development of guidelines and recommendations. The framework should address which guidelines are a priority, how the guidelines should be developed and which areas might be impacted, as well as the acceptability metrics or success factors;
- ▶ Engage in efforts (e.g. via standardisation activities) for achieving greater global alignment with other regulators (e.g. FDA) on these topics;
- ▶ Implement the priority recommendations of the HMA-EMA joint Big Data Task Force in the area of analytics.

### **3.2.1 Leverage non-clinical models and 3Rs principles**

Non-clinical models of the effects of medicines, such as improved use of tests based on human cells and organoids and in-silico modelling for early drug discovery are the subject of much ongoing research and have the potential to benefit drug development and support early efficacy studies. They are closely linked to the 3Rs concept, intended to replace, reduce and refine animal testing.

To date, the uptake of these newer models in marketing authorisation submissions has not been high, although substantial reductions in the number of animal tests in some areas have been achieved. One reason for hesitancy may be concerns on the part of developers as well as industry that use of such New Approach Methodologies (NAMs) will not be acceptable to regulators and will thus stall approvals. Other possible reasons for the limited use of NAMs include a lack of knowledge regarding the existence or the exact functioning of such models, lack of model validation, or high costs associated with their implementation. Encouragement of these techniques is therefore needed, including promoting earlier interaction with developers of NAMs, fostering communication with regulatory agencies and relevant EU/international stakeholder platforms, facilitating access to the SA qualification procedure and making use of digital tools and data standards.

To support the leveraging of non-clinical models and 3Rs principles EMA proposes to:

- ▶ Stimulate developers to use novel pre-clinical models where appropriate, including those adhering to the 3Rs:

- » Cooperate with other EU agencies/bodies to fund research and (access to) standardised repositories for alternative methods and models;
- » Development of clear guidance to encourage and prioritise the use of NAMs that can be used to fulfil testing requirements in lieu of traditional animal tests and that take the 3Rs into serious consideration;
- ▶ Re-focus the role of the Joint 3Rs working group (J3R WG) to support qualification of new alternative 3R-compliant methods/models including in silico and novel in vitro assays;
- ▶ Implement/develop IT tools to exploit the added value of SEND for the re-analyses of non-clinical studies to support clinical trials, marketing authorisation and improved evidence generation.

### **3.2.2 Foster innovation in clinical trials**

Innovation in clinical trials offers the opportunity to demonstrate the benefits of medicines that could not be shown by more conventional methods. It does this through more effective and efficient research, involving broader groups of medicines, patients, and researchers, and improving patient-centred access to medicines.

Innovation may come, for example, through the use of novel trial designs, endpoints, or techniques for gathering data, or the use of new techniques such as 'omics' and real-world data to stratify populations or disease taxonomy. Drivers for such innovation include small eligible patient populations, limited endpoints to demonstrate efficacy and benefit-risk, and the

availability of new data sets from digital technologies, e.g., patient reported outcomes captured by new technologies such as wearables. Moreover, clinical trials need to involve neglected populations including the elderly and pregnant women so they too can benefit more directly from research.

Novel designs and data sources require adapted statistical methodologies for their planning and analysis. New endpoints may need to be developed (for example when disease-modifying treatments replace symptomatic ones) and new biomarkers to support bridging of surrogate endpoints in early development to clinical endpoints in confirmatory studies.

Regulators will need to work with stakeholders and other bodies involved to ensure that innovative designs and approaches to trial conduct and analysis meet the needs of all. Novel approaches are needed to enable submission, assessment, authorisation and ongoing supervision of new trial designs throughout their lifecycle, as well as their design conduct, analysis and reporting of results. Patient perspectives are particularly important, and their involvement can greatly improve trial design and conduct, and the usefulness of the results and medicines developed.

Improving guidance on the design, conduct and analysis of clinical trials through broad stakeholder engagement, including patients and researchers can build a sound basis for advancing international consensus and its harmonisation via organisations such as ICH.

The sharing and use of information on trial design and conduct, and on the results of clinical trials, stimulates and accelerates innovation as well as building trust and understanding of the clinical trial process and its outcomes. This in turn supports increased participation by researchers and patients. Building on such stakeholder involvement and information sharing can enable training and promote acceptance of changes in clinical trial design and conduct.

Innovation in clinical trials also advances research and expertise across the European Research Area, both through the clinical trials themselves, and by driving basic research on areas such as new endpoints, new types of medicines, modes of action and manufacturing technologies.

To foster innovation in clinical trials, the Agency proposes the following actions:

- ▶ Establish a multi-stakeholder, neutral, platform, to enable new approaches to clinical studies and to position the EU as a preferred location for innovative clinical research;
- ▶ Drive development and adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance at EU and international level;
- ▶ Work with stakeholders, the EU Medicines Regulatory Network and the European Commission to promote and facilitate the conduct of complex clinical trials and other innovative clinical trial designs;
- ▶ Promote increased information sharing on clinical trial design, conduct, results and best practices. Build on this information and the multi-stakeholder platforms to enable further education, training and sharing of best practice in order to accelerate innovative change;
- ▶ Critically assess the clinical value of new and emerging endpoints and their role in facilitating patients' access to new medicines;
- ▶ Promote the inclusion of neglected populations such as pregnant women, the elderly and those of diverse ethnicity in clinical trials.

### **3.2.3 Develop the regulatory framework for emerging clinical data generation**

In the next few years, the use of digital technologies in clinical trials is expected to have a major impact not only on the way data are produced and collected, but also on the nature of the data itself. This includes continuous monitoring of variables, enhanced use of patient reported outcomes, and integration of 'big data' into the regulatory dataset. Data quality should be ensured, to avoid jeopardising the validity of the data collected in this way. The source, rate and volume of data collected by these methods means it is not always amenable to classical methods of statistical analysis, and that additional considerations may be needed to understand the import, for

example, of outliers, missing data, and fluctuations in the continuous monitoring.

Patient and HCP input is fundamental to the development and uptake (ease of use and compliance) of the technologies: clinical trial access might be improved by patient convenience and remote participation, but at the same time patients or centres might be excluded by unavailability of the technology, undermining the external validity of the trial. Training and best use practices are important tools in the development of the technologies. Data privacy and security are also extremely important considerations. Therefore, it is necessary to capitalise on existing expertise in public health institutions so that regulatory science requirements and impacts can be properly considered, and a suitable regulatory framework developed.

To develop a regulatory framework fit for emerging clinical data generation, the Agency proposes that regulators should:

- ▶ Develop methodology to incorporate clinical care data sources in regulatory decision-making;
- ▶ Clarify questions on data ownership and data security;
- ▶ Modernise the GCP regulatory oversight to enable decentralised models of clinical trials coupled with direct digital data accrual;
- ▶ Develop the capability to assess complex datasets captured by technology such as wearables;
- ▶ Facilitate training and understanding of healthcare professionals and patients to access and participate effectively in such trials;
- ▶ Support the development of robust digital endpoints through qualification, scientific advice, and the establishment of a multi-stakeholder platform to obtain feedback on their utilisation.

### **3.2.4 Expand benefit-risk assessment and communication**

Regulators and other stakeholders have developed and implemented structured benefit-risk frameworks to aid decisions and communication about benefits,

harms and uncertainties. New approaches are continuously being explored, and best practices are being developed across a variety of settings, from clinical trials to decision-making. There is, therefore, a need to continually consider the optimal tools to communicate regulatory benefit-risk assessment and support subsequent decision making.

Health economic considerations play a major role in determining patient access to medicines. Regulators should continue striving to quantify and communicate systematically benefits and harms, trade-offs, and uncertainties at the time of approval, to inform these downstream decisions. This is expected to bridge the gap between regulatory approval and access.

There is much interest from regulators and other stakeholders in developing ways to systematically incorporate patient-reported outcomes and patient preferences into drug development and the evaluation of benefit, harms, and uncertainties. This is expected to foster patient-centred drug-development and transparency about regulatory decisions. However, without regulatory guidelines for their assessment and application, their impact is often limited.

Patient-level data are not commonly analysed by regulators in the EU network. However, developing this capability could provide more robust and independent analyses of the data, more efficient data exploration, enable regulators to analyse data across products, and in general maximise the impact of the available data. Developing this capability in the EU network, however, is complex and requires careful analysis of feasibility and sustainability.

The Agency therefore proposes to implement the following actions:

- ▶ Include patient preferences to inform the benefit-risk assessment:
  - » Develop guidance building on recent developments (e.g., IMI PREFER) of appropriate methods for patient preference study design, conduct, analysis, and presentation for regulatory purposes, ensuring high quality methodology and independence;
  - » Provide guidance on the roles of patient preferences in the different therapeutic

contexts and regulatory decisions, i.e., how preferences can help regulators interpreting clinical trial outputs, how they can inform shared decision-making; how to handle heterogenous or conflicting preferences; how to communicate patient preferences in regulatory decisions;

- ▶ Promote systematic application of structured benefit-risk methodology and quality assurance systems in the approach to assessment and consistency of decision-making;
- ▶ Enhance structured assessment of benefits, harms, and uncertainties to improve communication to the public;
- ▶ Develop the capability for analysing individual patient data to support decision-making;
- ▶ Improve communication with HTAs and payers regarding therapeutic context, comparison vs. placebo/active-control, patient perspective.

### 3.2.5 Invest in special populations initiatives

Social and demographic changes in Europe are driving renewed efforts to address public health needs in special populations (e.g., the elderly, children, childbearing and breastfeeding women). Action in geriatric medicine has led to increased awareness of the issue in medicines assessments, and work on drug safety in pregnancy and breastfeeding is also ongoing. Furthermore, in areas of high unmet medical need where it is difficult to collect data via traditional routes an adaptive approach is being fostered to support novel preclinical and clinical trial designs as well as an iterative development in specific patient populations, gathering evidence through real-life use to supplement clinical trial data and early involvement of patients and health-technology-assessment bodies in discussions on a medicine's development.

The current regulatory framework for paediatric medicines, which has now been in place for just over 10 years, has had a positive impact on paediatric medicines development, but there is further to go in providing the evidence needed to improve medicines availability and safety for special populations. In practice, there are for example still areas in

paediatrics with a specifically high unmet need such as oncology and neonatology, new marketing applications still often fail to include sufficient data from elderly patients, and work in understanding the consequences of medicines exposure in the preconception period, during pregnancy and breastfeeding needs to be intensified and broadened.

The Agency proposes the following actions:

- ▶ Focus on accelerating access for patient (sub-) populations in urgent need whilst ensuring high quality data to evaluate efficacy and safety of medicines;
- ▶ Identify areas of highest unmet needs where clinical care data can supplement clinical trial data;
- ▶ Foster input of patients/patient representatives and carers in the regulatory process and enhance multi-stakeholder advice in collaboration with patients, HCPs, payers and HTAs;
- ▶ Progress implementation of the geriatric medicines strategy;
- ▶ Progress implementation of the joint EMA/EC paediatric medicines action plan:
  - » Participate in multi-stakeholder initiatives on neonatal medicines to further the understanding of disease mechanisms and natural history and develop models of disease progression to support innovative clinical trial design, biomarkers and endpoints that accurately capture treatment benefit;
  - ▶ Develop a strategic initiative in maternal-foetal health with other regulators and international stakeholders, to advance access through better understanding and communication of benefits, risks, and uncertainties of medicines use in pregnancy and breastfeeding:
    - » Such an initiative should include considerations regarding PK/PD modelling, epigenetics, reproductive toxicity studies, clinical trial design as well as post-authorisation follow-up methods;

- ▶ Encourage research to improve the efficiency and effectiveness of detecting drug safety issues (signal detection) in pregnant women and the elderly.

### 3.2.6 Optimise capabilities in modelling, simulation and extrapolation

Modelling and simulation (or model-informed drug development – MIDD) offer a quantitative framework for prediction and extrapolation. They generate knowledge and inference from integrated models of compound, mechanism and disease level data.

Extrapolation is the framework that promotes the use of quantitative methods, such as modelling and simulation, to help assess the relevance of existing information in one or more source populations to one or more target population(s) in respect of the disease, the drug pharmacology and clinical response to treatment.

Both frameworks enable optimal design and conduct of experiments, improve decision making, and consequently achieve gains in terms of timely access to patients and resources.

To increase the uptake of these approaches, there is a need for consensus on standards and their acceptability for regulatory, HTA and payers' decision making. In addition, dialogue with patients and healthcare professionals is necessary. In parallel, increasing the Agency's focus on quantitative methods for decision making requires increased capacity and organisational and workflow changes. The Agency is also expected also to play a role in facilitating data sharing and collaborations with external expert groups.

EMA therefore proposes the following actions:

- ▶ Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects;
- ▶ Develop guidance and standards on the use of AI in modelling and simulation for regulatory submissions;

- ▶ Deploy advances in RWD, modelling, simulation and extrapolation to benefit special populations particularly neglected patient populations;
- ▶ Promote development and international harmonisation of methods and standards via a multi-stakeholder platform;
- ▶ Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange:
  - » Invest in Centres of Excellence in regulatory science at an EU level, to work with regulatory agencies to provide training and research on modelling & simulation tools;
  - » Enhance collaboration with external partners/ consortia with expertise in modelling and simulation, and EU funded or co-founded projects e.g. IMI, Horizon 2020;
- ▶ Investigate possibilities for conducting modelling and simulation analyses to address key regulatory questions as part of product specific assessment or development of guidelines and policies;
- ▶ Consider working with stakeholders to foster data sharing through developing data standards and platforms for data exchange.

### 3.2.7 Exploit digital technology and artificial intelligence in decision making

The increasing rate at which data is being generated from a wide range of sources (so-called Big Data) poses challenges and opens opportunities. New methods, incorporating artificial intelligence, and new digital technologies and infrastructures, specialise in the processing and analysis of large, structured and unstructured datasets, and offer novel ways to extract and infer information. EMA plans to exploit these methods and technology to increase efficiency and inform regulatory decision-making. Developing guidance to regulate the associated privacy, ethical, transparency, explainability, trustworthiness and auditing aspects is of utmost importance to foster their acceptability.



Even though new methods incorporating AI capabilities and new digital technologies are rapidly advancing in other industries, these are still in their infancy in the pharmaceutical domain; there is a need to increase the network skills and capabilities on how to use cognitive computing tools to accelerate our ability to turn big data into meaningful scientific insight and activity. To ensure such tools and techniques are effective and appropriate for use, they will need to be developed through close collaboration between multi-disciplinary scientists and computer scientists. Global collaboration with EC, EU and international regulators, industry, HTAs, notified bodies, patients, healthcare professionals, academia, standardisation bodies is essential to achieve full incorporation of these new methods and tools in the regulatory framework. The implementation of the priority recommendations of the HMA-EMA joint Big Data Task Force can represent the first concrete step.

To exploit digital technology and artificial intelligence in decision making, it is proposed to:

- ▶ Establish a digital innovation lab to explore, pilot and develop solutions and processes, across the drug regulation spectrum, that leverage novel digital technology and artificial intelligence to support increase in efficiency and regulatory decision-making;
- ▶ Develop capacity and expertise across the regulatory network through curriculum development and knowledge-sharing initiatives on data science, digital technologies and artificial intelligence- related solutions, products and endpoints, and their applications in the regulatory system;
- ▶ Create and maintain a Health Data Science and AI forum to engage with a diverse set of stakeholders in novel digital technologies and artificial intelligence. This will include the technical, ethical, legal, regulatory and scientific perspectives of the use of digital technologies, and AI-powered applications;
- ▶ Establish a dedicated framework for the development of guidelines and recommendations. The framework should address which guidelines are a priority, how the guidelines should be developed, and which areas

might be impacted, as well as the acceptability metrics or success factors;

- ▶ Engage in efforts (e.g. via standardisation activities) for achieving greater global alignment with other regulators (e.g. FDA) on these topics;
- ▶ Implement the priority recommendations of the HMA-EMA joint Big Data Task Force in the area of analytics.

### 3.3 Goal 3: Advancing patient-centred access to medicines in partnership with healthcare systems

Patients and healthcare actors should be at the centre of the regulatory system’s actions, so an important strategic goal proposed for this strategy is to advance access to medicines. The public health aim is to ensure that patients receive timely access to affordable medicines that meet their medical needs, and that all players involved in healthcare have the information they need to guide correct prescription and use.

This will require EMA to build on its existing frameworks that bring together stakeholders at all levels of the decision-making chain, including, importantly, patients and healthcare professionals themselves. Cooperation will also be needed to ensure that real-world data, or more broadly ‘big data’, meet the needs of all stakeholders including HTAs and payers and can be used in the service of this goal.

Beyond data use, capitalising on the success of biosimilars will further advance access. Additionally, in order to ensure that patients can make informed decisions about the medicines to which they have access, improved communication, such as moves towards the delivery of electronic product information for patients and healthcare professionals, will be needed.

#### Summary table

| Advancing patient-centred access to medicines in partnership with healthcare systems     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                     | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Contribute to HTA’s preparedness and downstream decision making for innovative medicines | <ul style="list-style-type: none"><li>▶ Ensure the evidence needed by HTAs and payers is incorporated early in drug development plans, including requirements for post-licensing evidence generation;</li><li>▶ Enable information exchange with HTAs to support bridging from benefit-risk to relative effectiveness assessment;</li><li>▶ Discuss with HTAs guidance and methodologies for evidence generation and review;</li><li>▶ Collaborate with HTAs on the identification of priority products and technologies;</li><li>▶ Monitor the impact of decision-maker engagement through reviews of product-specific experience;</li><li>▶ Further develop the structured interaction between EMA and HTA bodies, respecting the respective remits.</li></ul> |

**Bridge from evaluation to access through collaboration with payers**

- ▶ Enable involvement of payers' requirements in the prospective discussion of evidence generation plans, including post-licensing evidence generation;
- ▶ Contribute to the preparedness of healthcare systems by creating opportunities for collaboration on horizon scanning;
- ▶ Establish more structured interaction between EMA and payers to support information flow, whilst respecting remits;
- ▶ Collaborate with stakeholders to monitor the performance (safety and effectiveness) of products newly launched on the market (learning healthcare system), and link to the planning of evidence through risk management plans (RMPs).

**Reinforce patient relevance in evidence generation**

- ▶ Revise the existing patient engagement methodology and review and update EMA's existing 'Framework for interaction with patients and patient organisations' to reflect EMA's evolving approach to patient data and enhanced patient involvement in EMA scientific committees;
- ▶ Explore and deploy additional methodologies to collect and use patient data for benefit-risk assessment;
- ▶ Update existing, and develop new EMA guidelines on patient data collection;
- ▶ Coordinate the approach to patient reported outcomes (PROs);
- ▶ Promote use of core health-related quality-of-life PROs.

**Promote use of high-quality real-world data (RWD) in decision-making**

- ▶ The actions in this Regulatory Science Strategy relating to RWD are included within the 10 actions listed under Big Data. In addition, specific pilots of RWD analytics will be conducted and work on pharmacovigilance methods will continue:
  - » Conduct a pilot of using rapid analytics of real-world data (including electronic health records) to support decision-making at the PRAC and CHMP;
  - » Review of the utility of using electronic health records for detecting drug safety issues (including drug interactions);
- ▶ Mapping of good examples of use of RWD in different phases of drug development to develop guidance on such use.

**Develop network  
competence  
and specialist  
collaborations to  
engage with big data**

- ▶ Deliver a sustainable platform to access and analyse healthcare data from across the EU (Data Analysis Real World Interrogation Network -DARWIN). Build the business case with stakeholders and secure funding to establish and maintain a secure EU data platform that supports better decision-making on medicines by informing those decisions with robust evidence from healthcare;
- ▶ Establish an EU framework for data quality and representativeness. Develop guidelines, a strengthened process for data qualification through Scientific Advice, and promote across Member States the uptake of electronic health records, registries, genomics data, and secure data availability;
- ▶ Enable data discoverability. Identify key meta-data for regulatory decision-making on the choice of data source, strengthen the current ENCePP resources database to signpost to the most appropriate data, and promote the use of the FAIR principles (Findable, Accessible, Interoperable and Reusable);
- ▶ Develop EU Network skills in Big Data. Develop a Big Data training curriculum and strategy based on a skills analysis across the Network, collaborate with external experts including academia, and target recruitment of data scientists, omics specialists, biostatisticians, epidemiologists, and experts in advanced analytics and AI;
- ▶ Strengthen EU Network processes for Big Data submissions. Launch a 'Big Data learnings initiative' where submissions that include Big Data are tracked and outcomes reviewed, with learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods;
- ▶ Build EU Network capability to analyse Big Data. Build computing capacity to receive, store, manage and analyse large data sets including patient level data (PLD), establish a network of analytics centres linked to regulatory agencies, and strengthen the Network ability to validate AI algorithms;
- ▶ Modernise the delivery of expert advice. Build on the existing working party structure to establish a Methodologies Working Party that encompasses biostatistics, modelling and simulation, extrapolation, pharmacokinetics, real world data, epidemiology and advanced analytics, and establish an Omics Working Party that builds on and reinforces the existing pharmacogenomics group;
- ▶ Ensure data are managed and analysed within a secure and ethical governance framework. Engage with initiatives on the implementation of EU data protection regulations to deliver data protection by design, engage with patients and healthcare professionals on data governance, and establish an Ethics Advisory Committee;

**Develop network competence and specialist collaborations to engage with big data**

- ▶ Collaborate with international initiatives on Big Data. Support the development of guidelines at international multilateral fora, a data standardisation strategy delivered through standards bodies, and bilateral collaboration and sharing of best practice with international partners;
- ▶ Create an EU Big Data 'stakeholder implementation forum'. Dialogue actively with key EU stakeholders, including patients, healthcare professionals, industry, HTA bodies, payers, device regulators and technology companies. Establish key communication points in each agency and build a resource of key messages and communication materials on regulation and Big Data.

**Deliver improved product information in electronic format (ePI)**

- ▶ Enable real-time interactivity within the Summary of Product Characteristics and Patient Leaflet;
- ▶ In conjunction with healthcare providers, patients and pharmaceutical industry representatives, develop a strategic plan to deliver a sustainable ePI system;
- ▶ Enable the reuse of structured medicinal product information by third parties through development of trustworthy source(s) and a standardised interface for access;
- ▶ Address the need for improvements in PI content, such as package leaflet layout and readability, and user testing, identified in the EC report;
- ▶ Plan for interoperability and interactivity of ePI with other eHealth systems and telematics initiatives, ensuring data portability;
- ▶ Explore how digitalisation of medicines information could be harnessed to address key EU Network priorities, such as initiatives to avoid and manage supply problems.

**Promote the availability and support uptake of biosimilars in healthcare systems**

- ▶ Further develop strategic communication campaigns to healthcare providers and patient organisations to reinforce trust and confidence;
- ▶ Enhance training of non-EU regulators in the evaluation of biosimilars with extension to all therapeutic areas;
- ▶ Address regulatory challenges in manufacturing e.g., statistical assessment of CQAs in the comparability exercise and the evolution of multisource biologicals/biosimilars;
- ▶ Further develop the biosimilar framework, adapting the clinical part of the development to the latest scientific knowledge concerning the comparability assessment.

**Further develop external engagement and communications to promote trust and confidence in the EU regulatory system**

- ▶ Develop content strategy in key public health areas and hot topics in regulatory science:
  - » Enhance professional outreach through scientific publications & conferences;
  - » Design communication campaigns in collaboration with relevant stakeholders to proactively approach to key public-health areas (e.g. vaccines);
  - » Improve communications for patients, healthcare professionals and other stakeholders including HTAs and payers;
- ▶ Develop more targeted and evidence-based communication facilitated by updated web content and format;
- ▶ Conduct research on optimising the impact of risk communication in changing the behaviour of patients and healthcare professionals, including as part of risk management and pharmacovigilance.

### **3.3.1 Contribute to HTA's preparedness and downstream decision making for innovative medicines**

Access to medicines does not depend solely on regulatory decisions: HTA bodies and payers also play key roles in determining medicines use and availability in EU healthcare systems. In order to advance patient access to innovative medicines, it is clear that these key players need to work even more closely together, while respecting each other's remit and perspectives. This also includes engagement of patient and healthcare professionals. Overall, such cooperation promotes preparedness of the healthcare systems for innovation and upcoming technologies.

Initiatives are already in place to try to ensure that the evidence generated during development of a medicine is relevant to the needs of all subsequent decision makers. These will need to be expanded, with particular focus on the planning of post-licensing evidence generation. Aligning evidence requirements contributes to faster patient access. Regulators must also ensure, through engagement with HTAs and other stakeholders, that new standards and guidelines are developed to meet scientific and technical advances. Collaboration on priority setting and identifying areas where engagement is particularly beneficial will help guide resource

allocation. A robust and effective framework for collaborative, EU-level cooperation is expected to streamline procedures, avoid duplication, shorten time for decision-making, and make the best use of human and financial resources, both public and private.

The Agency therefore proposes to implement the following actions:

- ▶ Ensure the evidence needed by HTAs and payers is incorporated early in drug development plans, including requirements for post-licensing evidence generation;
- ▶ Enable information exchange with HTAs to support bridging from benefit-risk to relative effectiveness assessment;
- ▶ Discuss with HTAs guidance and methodologies for evidence generation and review;
- ▶ Collaborate with HTAs on the identification of priority products and technologies;
- ▶ Monitor the impact of decision-maker engagement through reviews of product-specific experience;



- ▶ Further develop the structured interaction between EMA and HTA bodies, respecting the respective remits.

### 3.3.2 Bridge from evaluation to access through collaboration with payers

The introduction of innovative medicines into healthcare systems requires decisions by other bodies than regulators. Even if innovative medicines receive a marketing authorisation, difficulties in obtaining reimbursement can lead to delayed or no access for patients. There is therefore a clear need for exchange of information between regulators and payers.

It is recognised that the remits and criteria for decision making for regulators and payers are very different and need to be carefully respected. Determining the value of a medicine follows regulatory decision making but is based in the specific healthcare context. However, there remain areas that can benefit from relevant and adequate engagement.

Interaction to-date has been somewhat fragmented: since payment models vary so much across the EU, a single platform for such dialogue would be desirable. This would allow exploring ways to share horizon scanning activities (key to understanding future resource implications), and discussions on evidence generation with HTAs: the ultimate aim of the latter would be to enable one single evidence generation plan to collect the information needed by decision-makers. Understanding evidence requirements in areas of unmet medical need may be particularly relevant. It is also important for regulators to share information on the rationale for the populations eligible for treatment with a medicine, as the size of the eligible population can have a major impact on payment decisions.

To help move more smoothly from evaluation to access, EMA proposes the following actions to enhance collaboration with payers:

- ▶ Enable involvement of payers' requirements in the prospective discussion of evidence generation plans, including post-licensing evidence generation;

- ▶ Contribute to the preparedness of healthcare systems by creating opportunities for collaboration on horizon scanning;
- ▶ Establish more structured interaction between EMA and payers to support information flow, whilst respecting remits;
- ▶ Collaborate with stakeholders to monitor the performance (safety and effectiveness) of products newly launched on the market (learning healthcare system), and link to the planning of evidence through risk management plans (RMPs).

### 3.3.3 Reinforce patient relevance in evidence generation

Patients bring their experience, knowledge and expertise to scientific discussions on medicines and on the impact of regulatory decisions. EMA incorporates the patient voice all along the regulatory lifecycle of a medicine, reflecting the importance the Agency places on such engagement.

EMA is looking to further enhance its methods to enable greater input from the wider patient community in a systematic manner. There are also opportunities arising from new digital tools and the science of patient reporting. EMA is starting to see the use of various patient-reported outcomes (PROs, the reporting of functioning, disease state, or treatment) as endpoints within submissions for marketing authorisation applications for medicines. Given other trends such as eHealth, precision medicine and the drive for outcome-based healthcare, the use of patient data will likely continue to grow. Understanding how to generate, analyse and use relevant patient data will be key for EMA's regulatory science strategy.

- ▶ Revise the existing patient engagement methodology and review and update EMA's existing 'Framework for interaction with patients and patient organisations' to reflect EMA's evolving approach to patient data and enhanced patient involvement in EMA scientific committees;
- ▶ Explore and deploy additional methodologies to collect and use patient data for benefit-risk assessment;

- ▶ Update existing, and develop new EMA guidelines on patient data collection;
- ▶ Coordinate the approach to patient reported outcomes (PROs);
- ▶ Promote use of core health-related quality-of-life PROs.

### 3.3.4 Promote use of high-quality real-world data (RWD) in decision-making

Real world data is currently used predominantly in the post-authorisation phase but there are opportunities for further application throughout the medicines lifecycle to help address some of the limitations of clinical trials. The Agency recognises the fundamental importance of clinical trials in the establishment of a products benefit risk, however, there is potential for benefit of using RWD to generate complementary evidence across the product life cycle.

It will be important to agree amongst stakeholders where RWD may add value into the assessment process. Given the often heterogeneous nature of the data sources, further work is also needed on the analytical and epidemiological methodologies needed to deliver robust evidence. There are additional needs to ensure security of the data, and governance models must ensure these.

The actions EMA proposes to promote the use of high-quality RWD in decision making are:

- ▶ The actions in this Regulatory Science Strategy relating to RWD are included within the 10 actions listed under recommendation 3.3.5. In addition, specific pilots of RWD analytics will be conducted and work on pharmacovigilance methods will continue:
  - » Conduct a pilot of using rapid analytics of real-world data (including electronic health records) to support decision-making at the PRAC and CHMP;
  - » Review of the utility of using electronic health records for detecting drug safety issues (including drug interactions);

- ▶ Mapping of good examples of use of RWD in different phases of drug development to develop guidance on such use.

### 3.3.5 Develop network competence and specialist collaborations to engage with big data

Rapid developments in technology have resulted in the capture of vast volumes of healthcare data generated daily in clinical care, in academic research and in the processes of daily life. These offer the promise of capturing a more holistic view of the patient and disease. If analysed appropriately, these new sources of data can create new evidence which has the potential to add significantly to the way the benefit-risk of medicinal products is assessed over their entire lifecycle.

However, regulators need to collaborate with relevant specialists to develop a deep understanding of the data, understand how it may be presented and how it should be analysed, and create guidelines on standards and validation to ensure it is robust enough for regulatory decision-making. Secure mechanisms to protect patient confidentiality in line with data protection legislation will be critical for securing patient trust.

The EMA Regulatory Science Strategy has been informed by the recommendations of the [HMA-EMA joint Big Data Task force](#) which were published on 20 January 2020. Therefore, to support the development of the necessary competences, the Agency proposes to do the following:

- ▶ Deliver a sustainable platform to access and analyse healthcare data from across the EU (Data Analysis Real World Interrogation Network -DARWIN). Build the business case with stakeholders and secure funding to establish and maintain a secure EU data platform that supports better decision-making on medicines by informing those decisions with robust evidence from healthcare;
- ▶ Establish an EU framework for data quality and representativeness. Develop guidelines, a strengthened process for data qualification through Scientific Advice, and promote across Member States the uptake of electronic health

records, registries, genomics data, and secure data availability;

- ▶ Enable data discoverability. Identify key meta-data for regulatory decision-making on the choice of data source, strengthen the current ENCePP resources database to signpost to the most appropriate data, and promote the use of the FAIR principles (Findable, Accessible, Interoperable and Reusable);
- ▶ Develop EU Network skills in Big Data. Develop a Big Data training curriculum and strategy based on a skills analysis across the Network, collaborate with external experts including academia, and target recruitment of data scientists, omics specialists, biostatisticians, epidemiologists, and experts in advanced analytics and AI;
- ▶ Strengthen EU Network processes for Big Data submissions. Launch a 'Big Data learnings initiative' where submissions that include Big Data are tracked and outcomes reviewed, with learnings fed into reflection papers and guidelines. Enhance the existing EU PAS register to increase transparency on study methods;
- ▶ Build EU Network capability to analyse Big Data. Build computing capacity to receive, store, manage and analyse large data sets including patient level data (PLD), establish a network of analytics centres linked to regulatory agencies, and strengthen the Network ability to validate AI algorithms;
- ▶ Modernise the delivery of expert advice. Build on the existing working party structure to establish a Methodologies Working Party that encompasses biostatistics, modelling and simulation, extrapolation, pharmacokinetics, real world data, epidemiology and advanced analytics, and establish an Omics Working Party that builds on and reinforces the existing pharmacogenomics group;
- ▶ Ensure data are managed and analysed within a secure and ethical governance framework. Engage with initiatives on the implementation of EU data protection regulations to deliver data protection by design, engage with patients and

healthcare professionals on data governance, and establish an Ethics Advisory Committee;

- ▶ Collaborate with international initiatives on Big Data. Support the development of guidelines at international multilateral fora, a data standardisation strategy delivered through standards bodies, and bilateral collaboration and sharing of best practice with international partners;
- ▶ Create an EU Big Data 'stakeholder implementation forum'. Dialogue actively with key EU stakeholders, including patients, healthcare professionals, industry, HTA bodies, payers, device regulators and technology companies. Establish key communication points in each agency and build a resource of key messages and communication materials on regulation and Big Data.

### **3.3.6 Deliver improved product information in electronic format (ePI)**

There is a need to improve how information on medicines is conveyed to patients and healthcare professionals. Following a report from the European Commission in March 2017 on shortcomings in the product information of EU medicines (i.e. summary of product characteristics, the package leaflet and labelling) and discussion with representatives of stakeholder groups and the European Commission, EMA developed an action plan to improve the EU product information. One key element in this plan is to explore how electronic formats can be used to improve access to medicines information by patients and healthcare professionals. This would allow for rapid updating on key safety or efficacy issues, and easier, quicker access to the right information at the right point in the treatment journey, resulting in more informed decisions and better adherence to treatment.

The EMA action plan also outlines actions on amending EU guidelines and templates to enhance the overall quality and readability of the package leaflet, improving patient input in developing and testing of package leaflets, promotion and exchanges of best practices and assessing the potential of a key information section.

EMA recommends that work to implement real-time electronic product information should be continued and developed, taking into account the [key principles on electronic product information for human medicines in the EU](#) agreed by EMA, national medicines regulators and EC together with all stakeholders in 2019. Actions on readability, patient input and content of the product information should also be progressed. The Agency will continue to liaise closely with stakeholders to achieve this aim, and proposes the following actions:

- ▶ Enable real-time interactivity within the Summary of Product Characteristics and Patient Leaflet;
- ▶ In conjunction with healthcare providers, patients and pharmaceutical industry representatives, develop a strategic plan to deliver a sustainable ePI system;
- ▶ Enable the reuse of structured medicinal product information by third parties through development of trustworthy source(s) and a standardised interface for access;
- ▶ Address the need for improvements in PI content, such as package leaflet layout and readability, and user testing, identified in the EC report;
- ▶ Plan for interoperability and interactivity of ePI with other eHealth systems and telematics initiatives, ensuring data portability;
- ▶ Explore how digitalisation of medicines information could be harnessed to address key EU Network priorities, such as initiatives to avoid and manage supply problems.

### **3.3.7 Promote the availability and support uptake of biosimilars in healthcare systems**

Biosimilars are biological medicines developed to be highly similar to another biological medicine already authorised in the EU (the reference medicine). By introducing competition with the originator medicine, they widen patient access to biological treatments by making them more affordable. The EU is the world leader in biosimilar regulation and approval and shares this expertise cooperatively with regulators

in other parts of the world. EMA is recommending that this knowledge base should continue to be developed, to ensure that quality, safe and effective biological medicines are available to EU citizens.

In the past, lack of understanding about the nature of biosimilar medicines and the way they are regulated has been identified as contributing to distrust in their use. EMA is already working with healthcare professionals and patients to better explain the science behind the development and regulation of these particular medicines, and this work will be taken forward as the network continues to develop its expertise in the area.

To this end EMA is proposing to:

- ▶ Further develop strategic communication campaigns to healthcare providers and patient organisations to reinforce trust and confidence;
- ▶ Enhance training of non-EU regulators in the evaluation of biosimilars with extension to all therapeutic areas;
- ▶ Address regulatory challenges in manufacturing e.g., statistical assessment of CQAs in the comparability exercise and the evolution of multisource biologicals/biosimilars;
- ▶ Further develop the biosimilar framework, adapting the clinical part of the development to the latest scientific knowledge concerning the comparability assessment.

### **3.3.8 Further develop external engagement and communications to promote trust and confidence in the EU regulatory system**

The Agency has been engaging with patient and healthcare professionals and issuing external communications since its inception. Dialogue with stakeholders continues to be critical to EMA's function as a regulator, and to further developing a culture of transparency. It must also respond to a growing demand for transparency and information, aided by the growth of new media platforms and communication tools.

In engaging and communicating with stakeholders, EMA is committed to principles of transparency,

independence and integrity, accountability, appropriate interaction, broad representation, effective communication, and continuous improvement. To meet these aims, the network must continue to share best practice and ensure consistency and use research to ensure that its approach is evidence-based and meets the information needs of its stakeholders.

EMA therefore proposes the following:

- ▶ Develop content strategy in key public health areas and hot topics in regulatory science:
  - » Enhance professional outreach through scientific publications & conferences;
  - » Design communication campaigns in collaboration with relevant stakeholders to proactively approach to key public-health areas (e.g. vaccines);
  - » Improve communications for patients, healthcare professionals and other stakeholders including HTAs and payers;
- ▶ Develop more targeted and evidence-based communication facilitated by updated web content and format;
- ▶ Conduct research on optimising the impact of risk communication in changing the behaviour of patients and healthcare professionals, including as part of risk management and pharmacovigilance.

### 3.4 Goal 4: Addressing emerging health threats and availability/therapeutic challenges

The mission of EMA is to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the EU. To this end, the public health aim of our fourth goal is to ensure that the regulatory system can respond effectively to address the need for, and availability of, medicinal products to tackle existing and emerging health threats.

In support of this goal, recommendations have been made in several areas. EMA will continue its commitment and preparedness planning to support global efforts to respond to public health threats, including its support for the development of new antibacterial agents and vaccines to tackle antimicrobial resistance. It will also support innovative approaches to the development, authorisation and monitoring of vaccines, and initiatives to improve communication on these and build public understanding and trust.

Another area to be addressed is the unavailability in the EU of authorised medicines, either because medicines are not marketed or due to supply disruptions. As unavailability can have many causes and is a global issue, the solutions will require cooperation at different levels, involving the full range of stakeholders and international partners. The investigation of established medicines, authorised for particular therapeutic indications, to see if they can be used in other indications is also an area of focus. This has the potential to reduce the time and expense of development and offer additional therapeutic options to patients. Availability of less expensive medicines may also be facilitated via validation of in-vitro and/or in-silico tools to demonstrate bioequivalence of complex generic products to the reference standard. The core recommendations are outlined below.

#### Summary table

| Addressing emerging health threats and availability/therapeutic challenges                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                         | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Implement EMA’s health threats plan, ring-fence resources and refine preparedness approaches | <ul style="list-style-type: none"><li>▶ Enhance coordination of scientific and regulatory activities within the EU network;</li><li>▶ Evaluate preparedness for emerging pathogens and ‘disease X’;</li><li>▶ Advance understanding of the role of novel technology in responding to emerging health threats, to ensure appropriate regulatory support and oversight;</li><li>▶ Work with EU regulatory partners to harmonise the regulatory framework for vaccine clinical trials, including during emergencies:<ul style="list-style-type: none"><li>» Strengthen collaboration with international partners and stakeholders on the identification, development, authorisation and post-authorisation follow-up of relevant medicinal products;</li><li>» Effective and timely communication to regulatory partners, healthcare professionals and the public;</li></ul></li></ul> |



|                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches</b> | <ul style="list-style-type: none"> <li>▶ Develop methodology for the surveillance and detection of abuse of medicines including of opiates (pharmacovigilance).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Continue to support development of new antibacterial agents and their alternatives</b>           | <ul style="list-style-type: none"> <li>▶ Encourage new business models that provide “pull” incentives or different approaches beyond the current “funding research” strategy in the EU, including financial schemes to sustain availability of new and old antibiotics;</li> <li>▶ In collaboration with HTAs and payers, define the evidence requirements for new antibacterial medicines;</li> <li>▶ Evolve regulatory guidance and support alternative approaches to new antibacterial drug development as well as innovative approaches for prevention and treatment of infections;</li> <li>▶ Support the development and application of rapid diagnostic tools;</li> <li>▶ Support initiatives, such as the clinical trials network, to facilitate and accelerate clinical development.</li> </ul>                                                                                                                                                                                                           |
| <b>Promote global cooperation to anticipate and address supply problems</b>                         | <ul style="list-style-type: none"> <li>▶ Build on deliverables from the work plan of the HMA/EMA Task Force on availability of authorised medicines;</li> <li>▶ Explore mechanisms to increase manufacturing capacity in Europe and internationally, in particular for essential medicines;</li> <li>▶ Enhance collaboration with international regulators in the area of supply disruptions due to manufacturing quality issues;</li> <li>▶ Promote greater knowledge exchange with international stakeholders on shortages due to quality/manufacturing issues;</li> <li>▶ Continue to engage with all stakeholders to address the causes and consequences of lack of medicines' availability;</li> <li>▶ Support international harmonisation of regulatory science standards for complex generic medicines addressing bioequivalence, waivers and modelling;</li> <li>▶ Improve monitoring of shortages and enhance communication of supply problems to EU citizens, their representatives and HCPs.</li> </ul> |

**Support innovative approaches to the development, approval and post-authorisation monitoring of vaccines**

- ▶ Establish a platform for EU benefit-risk monitoring of vaccines post-approval;
- ▶ Communicate proactively with key stakeholders on benefit-risk using evidence-based tools to tackle vaccine hesitancy;
- ▶ Examine innovative clinical trial approaches to expedite vaccine development;
- ▶ Advance methods/tools to characterise immune response and support definition of vaccine quality attributes;
- ▶ Foster the development of improved delivery systems based on novel technologies;
- ▶ Engage with public health authorities and NITAGs to better inform vaccine decisions;
- ▶ Advance understanding of the role of novel technology (such as platform technologies) in responding to emerging health threats, in order to ensure appropriate regulatory support and oversight;
- ▶ Harmonise the regulatory framework for vaccine clinical trials, including during emergencies.

**Support the development and implementation of a repurposing framework**

- ▶ Enhance scientific and regulatory advice on evidence generation and MAA submission;
- ▶ Develop methodological principles for third-party data-pooling, relevant RWD and historical non-clinical datasets;
- ▶ Translate experience with EMA's registry pilot to guide RWD collection;
- ▶ Explore utility of low-intervention clinical trials for evidence generation.

### **3.4.1 Implement EMA's health threats plan, ring-fence resources and refine preparedness approaches**

EMA has in place a multilevel health threats plan, making use of its coordination role within the EU network. Dedicated regulatory science advice and evaluation procedures have been set up to support the fast and effective development and oversight of medicines required to respond to a range of emerging health threats with a focus on biological threats from pandemic flu to the case of any currently unidentified pathogen (so-called 'disease X'). EU research programmes have also been put

in place to promote large-scale clinical research into infectious diseases and design manufacturing processes suitable for rapid delivery of tools such as vaccines and antibodies.

Recent experiences with Ebola, Zika, and the current outbreak of a novel coronavirus (COVID-19), on top of previous influenza pandemics and MERS/SARS, have shown the importance of international cooperation and close liaison and communication within the network and our stakeholders. This is true both for inter-epidemic periods and during an outbreak. In terms of preparedness, there is a need to define the scientific evidence to allow regulatory

evaluation of vaccines and other therapeutics in advance of an outbreak. In addition, resources will need to be proactively identified and ring-fenced to ensure that planned actions can be implemented promptly and effectively when needed.

The Agency therefore proposes the following actions:

- ▶ Enhance coordination of scientific and regulatory activities within the EU network;
- ▶ Evaluate preparedness for emerging pathogens and 'disease X';
- ▶ Advance understanding of the role of novel technology in responding to emerging health threats, to ensure appropriate regulatory support and oversight;
- ▶ Work with EU regulatory partners to harmonise the regulatory framework for vaccine clinical trials, including during emergencies:
  - » Strengthen collaboration with international partners and stakeholders on the identification, development, authorisation and post-authorisation follow-up of relevant medicinal products;
  - » Effective and timely communication to regulatory partners, healthcare professionals and the public;
- ▶ Develop methodology for the surveillance and detection of abuse of medicines including of opiates (pharmacovigilance).

### **3.4.2 Continue to support development of new antibacterial agents and their alternatives**

New antibacterial agents and other medicines for managing bacterial infections are badly needed as part of the 'One Health' approach to combat ever-increasing antimicrobial resistance. EMA is currently revising the guidance it provides to developers. International collaboration to harmonise regulatory requirements for approval will be key to allowing a single development plan. Development of clinical trials networks to facilitate development of new antibacterials should also be supported. Collaboration with HTAs and payers to ensure that the evidence

requirements for such new medicines also meet their needs is also vital.

EMA is also contributing to projects aimed at developing new business models and incentives for developers, to encourage development of antimicrobials for unmet needs and point-of-care diagnostics to ensure that antibacterials are used appropriately.

The Agency therefore proposes the following actions:

- ▶ Encourage new business models that provide "pull" incentives or different approaches beyond the current "funding research" strategy in the EU, including financial schemes to sustain availability of new and old antibiotics;
- ▶ In collaboration with HTAs and payers, define the evidence requirements for new antibacterial medicines;
- ▶ Evolve regulatory guidance and support alternative approaches to new antibacterial drug development as well as innovative approaches for prevention and treatment of infections;
- ▶ Support the development and application of rapid diagnostic tools;
- ▶ Support initiatives, such as the clinical trials network, to facilitate and accelerate clinical development.

### **3.4.3 Promote global cooperation to anticipate and address supply problems**

The unavailability of medicinal products in the EU is a topic of considerable concern for authorities, patient and consumer groups, healthcare providers and the pharmaceutical industry itself. Unavailability of medicinal products refers not only to supply chain disruptions (e.g. manufacturing problems) for authorised and/or marketed products but also to medicines where a marketing authorisation application is not made or is withdrawn, and authorised products that are never or no longer marketed. Availability of less expensive medicines may also be increased via validation of new tools to demonstrate bioequivalence of complex generic products to the reference standard.

The reasons for unavailability are therefore complex and, given the global nature of development and medicine supply chains, international cooperation is vital to address them. To further foster this, the Agency proposes to:

- ▶ Build on deliverables from the work plan of the HMA/EMA Task Force on availability of authorised medicines;
- ▶ Explore mechanisms to increase manufacturing capacity in Europe and internationally, in particular for essential medicines;
- ▶ Enhance collaboration with international regulators in the area of supply disruptions due to manufacturing quality issues;
- ▶ Promote greater knowledge exchange with international stakeholders on shortages due to quality/manufacturing issues;
- ▶ Continue to engage with all stakeholders to address the causes and consequences of lack of medicines' availability;
- ▶ Support international harmonisation of regulatory science standards for complex generic medicines addressing bioequivalence, waivers and modelling;
- ▶ Improve monitoring of shortages and enhance communication of supply problems to EU citizens, their representatives and HCPs.

### **3.4.4 Support innovative approaches to the development, approval and post-authorisation monitoring of vaccines**

Vaccines are among the most cost-effective and successful interventions in public health but they face specific regulatory challenges to develop and maintain availability. Because of their complexity, determination of quality attributes requires exploration of innovative tools and methods. New approaches to clinical development are equally warranted, as well as more fundamental research into the immune response and definition of immune markers and assays. This would be particularly beneficial in the light of novel emerging vaccine technologies and alternative routes of administration.

A more integrated dialogue between regulators and public health authorities is warranted to better inform vaccine development and decisions from competent authorities. Moreover, the creation of a platform for vaccine safety and effectiveness monitoring in the post-approval phase would be highly beneficial to both regulators and public health bodies. Regulators also have a key role in providing stakeholders and the wider public with information on the quality, efficacy and safety of vaccines and the way they are assessed and monitored, in order to help build public trust and overcome vaccine hesitancy. Again, cooperation with public health bodies in this aim is needed.

EMA therefore proposes the following actions:

- ▶ Establish a platform for EU benefit-risk monitoring of vaccines post-approval;
- ▶ Communicate proactively with key stakeholders on benefit-risk using evidence-based tools to tackle vaccine hesitancy;
- ▶ Examine innovative clinical trial approaches to expedite vaccine development;
- ▶ Advance methods/tools to characterise immune response and support definition of vaccine quality attributes;
- ▶ Foster the development of improved delivery systems based on novel technologies;
- ▶ Engage with public health authorities and NITAGs to better inform vaccine decisions;
- ▶ Advance understanding of the role of novel technology (such as platform technologies) in responding to emerging health threats, in order to ensure appropriate regulatory support and oversight;
- ▶ Harmonise the regulatory framework for vaccine clinical trials, including during emergencies.

### **3.4.5 Support the development and implementation of a repurposing framework**

Medical research is increasingly focusing on how existing medicines licensed for use in treating

particular conditions can also be investigated for use in treating other conditions. This has led to a series of discussions held at the European level via the STAMP Commission Expert Group, of which EMA is a member. These discussions focus particularly on seeking new indications for well established, or off patent medicines in areas of unmet medical need, so as to offer additional therapeutic options to patients, to reduce the time and costs of development by building on evidence already generated and to contribute a more sustainable health system.

Supporting repurposing requires consideration of several areas: the potential incentives and disincentives; the sources of evidence supporting re-purposing; the involvement of academia and not-for profit organisations (including patients organisations); introducing related changes to marketing authorisations as well as off-label use. Such consideration can only be achieved through developing ongoing multi-stakeholder discussions in a more formal framework.

To support the development and implementation of a framework for repurposing medicines, the Agency proposes:

- ▶ Enhance scientific and regulatory advice on evidence generation and MAA submission;
- ▶ Develop methodological principles for third-party data-pooling, relevant RWD and historical non-clinical datasets;
- ▶ Translate experience with EMA's registry pilot to guide RWD collection;
- ▶ Explore utility of low-intervention clinical trials for evidence generation.

### 3.5 Goal 5: Enabling and leveraging research and innovation in regulatory science

The Agency’s fifth goal is to develop the existing interaction between the EU regulatory network and academia further, in order to be kept informed of relevant scientific innovations and research and identify solutions to regulatory needs and challenges. This is the key to delivering the other strategic goals and recommendations laid out in the proposals.

It is envisaged that this aim will be achieved by establishing a novel regulatory science and innovation platform in partnership with academic research centres. The ultimate public health aim is to ensure that regulatory science remains at the cutting edge so that EMA can deliver its fundamental mission of protecting human and animal health and facilitating the availability of medicines to patients.

#### Summary table

| Enabling and leveraging research and innovation in regulatory science                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                                                           | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science | <ul style="list-style-type: none"><li>▶ Develop and implement a roadmap that clarifies, where and how partnerships with academia can best contribute to the human and veterinary RSS. This should build on existing networks and consider how best to support academics developing medicines while identifying practical actions that facilitate interaction at strategic, tactical and operational level;</li><li>▶ Identify, in consultation with research institutions, academia and other relevant stakeholders, fundamental research and associated training/ education topics in strategic areas of regulatory science relevant to patients (such as PROs, omics-based diagnostics, epigenetics, drug-device combinations, modelling and simulation, Big Data, and artificial intelligence);</li><li>▶ Proactively engage with DG Research &amp; Innovation, DG-SANTE, DG CONNECT, the Innovative Health Initiative, the ENVI Agencies and Member State funding agencies to propose and issue calls to establish research collaborations;</li><li>▶ Further develop research and evaluation of the impact of pharmacovigilance and risk management planning including:<ul style="list-style-type: none"><li>» Conduct, results and impact of post authorisation safety studies;</li><li>» Impact on labelling changes and utility for significant product issues evaluation of periodic safety update reports;</li><li>» Impact of different types of reports of suspected adverse drug reactions including spontaneously reported non-serious and patient reports in order to optimise detection of new safety issues;</li></ul></li></ul> |

|                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science</b>    | <ul style="list-style-type: none"> <li>» Impact research following major regulatory action where additional risk minimisation measures are introduced. Such research should include both quantitative and qualitative approaches.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions</b> | <ul style="list-style-type: none"> <li>▶ Ring-fence EMA funding to address rapidly emerging regulatory science research questions;</li> <li>▶ Ensure close interaction between network scientists, academia and learned societies to deliver tangible impact through translation of this applied research into new drug products and regulatory tools;</li> <li>▶ Actively engage, through these applied projects, in training early-career researchers in regulatory science (e.g., via placements within the network);</li> <li>▶ Create a bridging action plan to feed iterative and interactive engagements between these stakeholders as a core strategy of the EMA, National (HMA and EU-IN) and global (ICMRA) regulatory authorities.</li> </ul>                                            |
| <b>Identify and enable access to the best expertise across Europe and internationally</b>                                                | <ul style="list-style-type: none"> <li>▶ Explore the creation of a 'shared environment' in which novel insights and experiences are shared among all stakeholders, including innovator and generic (complex) drug manufacturers, regulatory bodies and academia;</li> <li>▶ For rare diseases, foster collaboration with European Reference Networks and propose a collaboration plan that includes definition of necessary resourcing and objectives;</li> <li>▶ Propose a framework that allows for adequate identification and involvement of independent experts and ensures a rigorous conflicts of interest policy;</li> <li>▶ Develop a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle.</li> </ul> |
| <b>Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders</b>                           | <ul style="list-style-type: none"> <li>▶ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient;</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |



**Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders**

- ▶ Collaborate with the EMRN to:
  - » Identify gaps in training and learning objectives;
  - » Work with academic institutions to build and provide regulatory training modules or courses;
- ▶ Conduct horizon scanning in key areas of innovation via collaborations with academia, the EU-Innovation Network and ICMRA;
- ▶ Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders.

### **3.5.1 Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science**

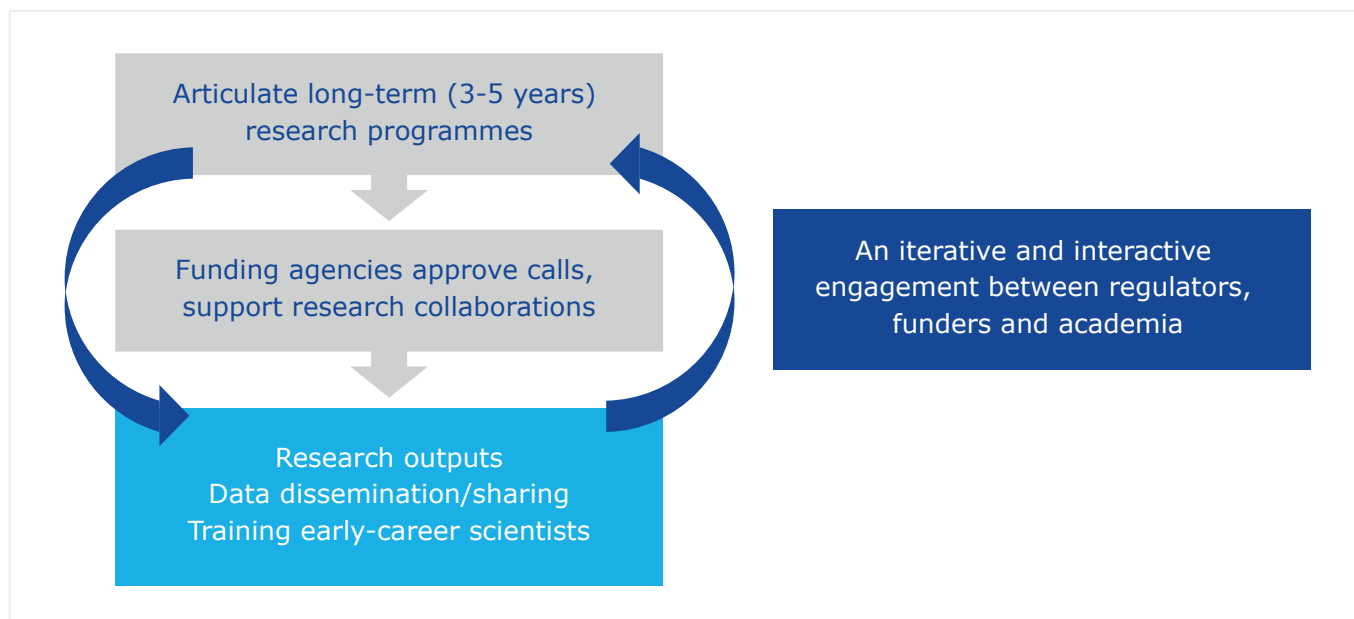
Life sciences research, much of which is relevant to medicines development, is strong in the EU. To enhance its impact, increased dialogue between scientists and regulatory authorities is crucial. With this in mind, more regular, iterative engagement will be developed between regulators, funders, and research centres in order to develop partnerships for research in selected areas of regulatory science.

The aim is to provide a mechanism for scientists in the regulatory network and research centres to collaborate in identifying and tackling important research questions. Such collaboration will ensure a coordinated approach across the EU network, so that regulatory decision-making and policy can be evidence-driven and consistent.

The Agency proposes the following actions:

- ▶ Develop and implement a roadmap that clarifies, where and how partnerships with academia can best contribute to the human and veterinary RSS. This should build on existing networks and consider how best to support academics developing medicines while identifying practical actions that facilitate interaction at strategic, tactical and operational level;
- ▶ Identify, in consultation with research institutions, academia and other relevant stakeholders, fundamental research and associated training/education topics in strategic areas of regulatory science relevant to patients (such as PROs, omics-based diagnostics, epigenetics, drug-device combinations, modelling and simulation, Big Data, and artificial intelligence);
- ▶ Proactively engage with DG Research & Innovation, DG-SANTE, DG CONNECT, the Innovative Health Initiative, the ENVI Agencies and Member State funding agencies to propose and issue calls to establish research collaborations;
- ▶ Further develop research and evaluation of the impact of pharmacovigilance and risk management planning including:
  - » Conduct, results and impact of post authorisation safety studies;
  - » Impact on labelling changes and utility for significant product issues evaluation of periodic safety update reports;
  - » Impact of different types of reports of suspected adverse drug reactions including spontaneously reported non-serious and patient reports in order to optimise detection of new safety issues;
  - » Impact research following major regulatory action where additional risk minimisation measures are introduced. Such research should include both quantitative and qualitative approaches.

**Figure 8.** Network-led partnerships with academia to undertake research in strategic areas of regulatory science



### 3.5.2 Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

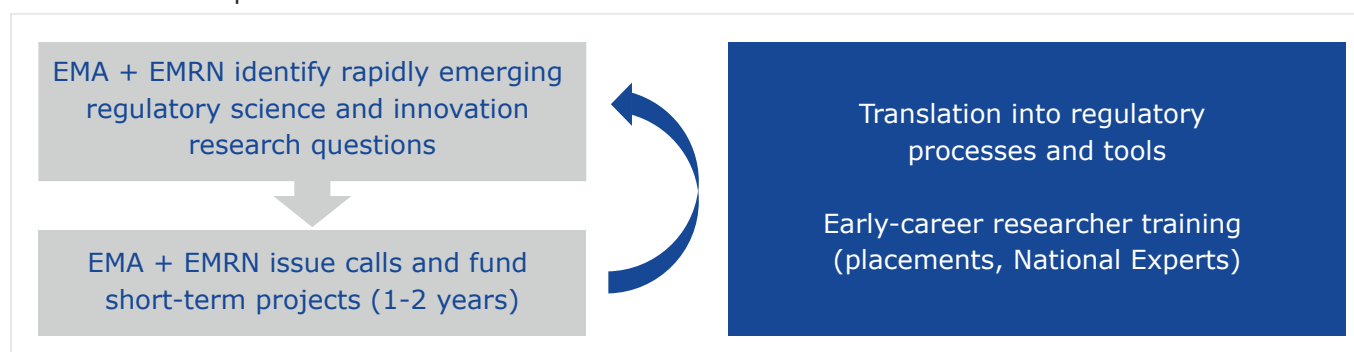
The collaboration in regulatory science above represents a platform that can also be applied to address, in a timely way, emerging innovations that require new regulatory competencies, methods, or tools.

The aim is to allow network scientists and academia to collaborate in exploring specific, evolving regulatory questions in order to develop the skills and tools that the network needs to respond. Resource capacity will need to be reserved to allow this.

To leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions, the Agency proposes to implement the following actions:

- ▶ Ring-fence EMA funding to address rapidly emerging regulatory science research questions;
- ▶ Ensure close interaction between network scientists, academia and learned societies to deliver tangible impact through translation of this applied research into new drug products and regulatory tools;
- ▶ Actively engage, through these applied projects, in training early-career researchers in regulatory science (e.g., via placements within the network);
- ▶ Create a bridging action plan to feed iterative and interactive engagements between these stakeholders as a core strategy of the EMA, National (HMA and EU-IN) and global (ICMRA) regulatory authorities.

**Figure 9.** Collaboration between academia and network scientists to address rapidly emerging regulatory science research questions



### 3.5.3 Identify and enable access to the best expertise across Europe and internationally

Understandably, the top experts in any field are in high demand as invited speakers at international meetings, as reviewers of grant applications and peer-reviewed journal publications, and as consultants to industry. Regulators too require access to the highest levels of expertise, and as scientific disciplines become ever more refined, this means competing for the skills and knowledge of a relatively small number of people.

The partnerships envisaged between the network and academia will naturally need to seek the best international expertise in key areas of regulatory science. It is essential, therefore, that access to such expertise be facilitated, by adopting a proportionate approach to potential conflicts of interest, to permit the best advice to be accessed in areas of innovation that are new to regulators and are becoming ever more specialised.

In order to implement this recommendation, the Agency proposes to do the following:

- ▶ Explore the creation of a 'shared environment' in which novel insights and experiences are shared among all stakeholders, including innovator and generic (complex) drug manufacturers, regulatory bodies and academia;
- ▶ For rare diseases, foster collaboration with European Reference Networks and propose a collaboration plan that includes definition of necessary resourcing and objectives;
- ▶ Propose a framework that allows for adequate identification and involvement of independent experts and ensures a rigorous conflicts of interest policy;
- ▶ Develop a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle.

### 3.5.4 Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders

The open exchange of knowledge is fundamental to science and a driver of progress. Such exchange, via a close partnership between the regulatory network and the expertise available in universities and research institutes, offers important benefits to both partners.

The development of high-quality learning materials in those basic and applied biomedical and social sciences that comprise regulatory science (i) will benefit the training needs of the network while (ii) at the same time improving the knowledge of academic groups and scientists working in the field of health research, thus enhancing the success and outcomes of academia driven clinical research and (iii) strengthening long term knowledge (about medicines development and regulatory science) during professional education and training (at both undergraduate and postgraduate levels) of the relevant scientific professions.

In order to implement this recommendation, the Agency proposes to do the following:

- ▶ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient;
- ▶ Collaborate with the EMRN to:
  - » Identify gaps in training and learning objectives
  - » Work with academic institutions to build and provide regulatory training modules or courses;
- ▶ Conduct horizon scanning in key areas of innovation via collaborations with academia, the EU-Innovation Network and ICMRA;
- ▶ Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders.



## 4. Veterinary medicines — four strategic goals for regulatory science

**Figure 10.** Veterinary strategic goals



EMA's vision is to continue fostering scientific excellence in the regulation of veterinary medicines for the benefit of animal and public health, while facilitating and promoting innovation and access to novel medicinal products.

To this end, four strategic goals are proposed, aligned to those envisaged for human medicines. Each is associated with a set of core recommendations and their underlying actions.



# 4.1 Goal 1: Catalysing the integration of science and technology in medicines development

Novel and innovative developments by definition enter uncharted regulatory territory. This means they face uncertainties regarding their progression which can inhibit their translation into new medicines. The aim of the first goal is to foster a more proactive approach by regulators like EMA, so as to reduce this uncertainty and help new science and technology to be incorporated into the development of veterinary medicines and allow the needs of animals and public health to be better met. To do this, capacity and expertise will have to be sought in new areas of innovation. Moreover, flexibility should be built into the implementation of the new veterinary legislation to enable some element of “future-proofing”. This cannot be done in isolation as the global nature of medicines development means that regulatory harmonisation at an early stage is needed. The core recommendations below go some way to achieving this.

## Summary table

| Catalysing the integration of science and technology in medicines development |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                          | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Transform the regulatory framework for innovative veterinary medicines        | <ul style="list-style-type: none"><li>▶ Produce further guidance to implement the annex to the new veterinary legislation (Regulation (EU) 2019/6) that defines proportionate and future-proofed technical standards for novel veterinary therapies, particularly biologicals;</li><li>▶ Ensure that the new regulatory environment is applied in a timely manner, in line with research for innovative products at national and European level provided through specific programs;</li><li>▶ Develop standards for novel therapies and the promotion of new endpoints for the evaluation of efficacy;</li><li>▶ Consider improving regulatory requirements for post-authorisation evidence generation for novel therapies;</li><li>▶ Strengthen support to developers throughout the development lifecycle of novel therapies;</li><li>▶ Contribute to, and share resources with, the human domain in the area of novel therapies, such as the approach to assessment of cell therapies, monoclonal antibodies, etc.;</li><li>▶ Increase EU network capacity and capability in novel therapies drawing on knowledge and training from human experience.</li></ul> |

**Reinforce and further embed application of the 3Rs principles**

- ▶ Apply the highest possible 3Rs standards when implementing the Veterinary Medicines Regulation (EU) 2019/6 as well as other legislative documents/guidelines to stimulate developers to use novel approaches adhering to 3Rs standards;
- ▶ Strengthen cooperation between all stakeholders and international partners:
  - » Cooperate with other EU agencies/bodies to fund research and (access to) standardised repositories for alternative methods and models;
- ▶ Promote in silico methodology (e.g. modelling), novel in vitro assays and systematic reviews to reduce animal use, particularly in toxicology/epidemiology and batch control:
  - » Re-focus the role of the Joint 3Rs working group (J3R WG) to support qualification of new alternative 3R-compliant method/models including in silico and novel in vitro assays;
  - » Development of clear guidance to encourage and prioritise the use of NAMs that can be used to fulfil testing requirements in lieu of traditional animal tests and that take the 3Rs into serious consideration;
- ▶ Promote regulatory acceptance and training.

**Facilitate implementation of novel manufacturing models**

- ▶ Recruit and develop expertise, in novel manufacturing technologies and develop training and tools to enhance the assessment process;
- ▶ Identify bottlenecks and propose modernisation of relevant regulations and guidance to facilitate novel manufacturing models, and novel approaches to traditional manufacturing. This should include guidance on strengthened early interaction, transparency and communication with stakeholders on regulatory requirements for novel manufacturing technologies;
- ▶ Address regulatory challenges in point-of-care manufacturing such as responsibility for the manufacturing process, the concept of batch control, and the role of the Qualified Person;
- ▶ Encourage the use of risk-based approaches to manufacturing processes and control strategies throughout the product lifecycle;
- ▶ Facilitate a flexible and fit for purpose approach in application of Good Manufacturing Practice with respect to novel therapies;
- ▶ Support the development of greener manufacturing technologies in line with the EU's 'Strategic Approach to Pharmaceuticals in the Environment'.

### 4.1.1 Transform the regulatory framework for innovative veterinary medicines

Current regulatory paradigms and technical requirements are not well adapted to the challenges presented by new types of veterinary medicines, and there is limited available expertise, both externally and within the EU network, to ensure consistent and informed scientific advice in the assessment process. There may be only a handful of experts in a new technology, and some of those might have a conflict of interest due to involvement with the product under consideration or with a competitor product. Ways must therefore be found to develop standards and increase the network's capacity to access the expertise required to properly assess novel veterinary products, while building in the safeguards needed to ensure that conflicts of interest are transparently recognised and addressed. This will involve learning from, and sharing resources with, the human domain. Importantly, EMA is also already cooperating closely with international partners, particularly FDA, in the area of novel technologies to share the limited veterinary expertise available.

To change the regulatory framework so that it can better support innovative veterinary medicines, the Agency therefore proposes the actions listed below:

- ▶ Produce further guidance to implement the annex to the new veterinary legislation (Regulation (EU) 2019/6) that defines proportionate and future-proofed technical standards for novel veterinary therapies, particularly biologicals;
- ▶ Ensure that the new regulatory environment is applied in a timely manner, in line with research for innovative products at national and European level provided through specific programs;
- ▶ Develop standards for novel therapies and the promotion of new endpoints for the evaluation of efficacy;
- ▶ Consider improving regulatory requirements for post-authorisation evidence generation for novel therapies;
- ▶ Strengthen support to developers throughout the development lifecycle of novel therapies;

- ▶ Contribute to, and share resources with, the human domain in the area of novel therapies, such as the approach to assessment of cell therapies, monoclonal antibodies, etc.;
- ▶ Increase EU network capacity and capability in novel therapies drawing on knowledge and training from human experience.

### 4.1.2 Reinforce and further embed application of the 3Rs principles

The use of animals in scientific procedures, including regulatory testing of human and veterinary medicinal products, is strictly controlled within the EU and the relevant legislation articulates the ultimate goal of replacing the use of all live animals for scientific and educational purposes as soon as it is possible to reasonably do so. The so-called '3Rs' approach envisages that animal testing should be replaced, reduced (minimising the number of animals used) and refined to minimise the pain and distress of the animals used.

Novel approaches in line with these principles—e.g. organs/systems on a chip and in-silico modelling—are the subject of much ongoing research and have the potential to benefit drug development and support early efficacy studies, as well as improving the predictive ability of (pre-)clinical testing systems. In addition to some well-established alternative methods, various novel techniques have been accepted by EU regulatory authorities and some have been incorporated in guidelines or European Pharmacopoeia monographs.

There may, however, be hesitancy on the part of developers to use such new methods in marketing authorisation applications because of concerns that they will not be acceptable to regulators and may therefore stall the approval process. Encouragement of these techniques is therefore needed.

- ▶ Apply the highest possible 3Rs standards when implementing the Veterinary Medicines Regulation (EU) 2019/6 as well as other legislative documents/guidelines to stimulate developers to use novel approaches adhering to 3Rs standards;
- ▶ Strengthen cooperation between all stakeholders and international partners:



- » Cooperate with other EU agencies/bodies to fund research and (access to) standardised repositories for alternative methods and models;
- Promote in silico methodology (e.g. modelling), novel in vitro assays and systematic reviews to reduce animal use, particularly in toxicology/epidemiology and batch control:
  - » Re-focus the role of the Joint 3Rs working group (J3R WG) to support qualification of new alternative 3R-compliant method/models including in silico and novel in vitro assays;
  - » Development of clear guidance to encourage and prioritise the use of NAMs that can be used to fulfil testing requirements in lieu of traditional animal tests and that take the 3Rs into serious consideration;
- Promote regulatory acceptance and training.

### 4.1.3 Facilitate implementation of novel manufacturing models

Technological development is allowing new and more efficient ways of manufacturing medicines. These new manufacturing methods include, for example, continuous manufacturing, an alternative to traditional batch processing in which raw materials are continually input at one end of the process and output materials continuously collected and additive manufacturing ("3D printing"), which is intended for the production of complex customised products designed to address the needs of an individual animal, including production on site, as well as processes employing innovative analytical technologies and technologies. Through innovative use of digital tools and data, these techniques offer an opportunity to reduce waste, produce medicines in more flexible and responsive ways and tailor production to specific, even individual, medical needs. Their implementation should therefore be facilitated by the regulatory system.

However, new manufacturing technologies for therapies such as stem cells, farm-specific vaccines and plant-based technologies fit poorly into the traditional regulatory models, and may require adaptation or changes to GMP requirements and standards and the development of specific regulatory

guidance and monitoring. In addition, regulators will need expertise to allow adequate oversight of the computer software used to control these new processes.

- Recruit and develop expertise, in novel manufacturing technologies and develop training and tools to enhance the assessment process;
- Identify bottlenecks and propose modernisation of relevant regulations and guidance to facilitate novel manufacturing models, and novel approaches to traditional manufacturing. This should include guidance on strengthened early interaction, transparency and communication with stakeholders on regulatory requirements for novel manufacturing technologies;
- Address regulatory challenges in point-of-care manufacturing such as responsibility for the manufacturing process, the concept of batch control, and the role of the Qualified Person;
- Encourage the use of risk-based approaches to manufacturing processes and control strategies throughout the product lifecycle;
- Facilitate a flexible and fit for purpose flexible approach in application of Good Manufacturing Practice with respect to novel therapies;
- Support the development of greener manufacturing technologies in line with the EU's 'Strategic Approach to Pharmaceuticals in the Environment'.

## 4.2 Goal 2: Driving collaborative evidence generation and improving the scientific quality of evaluations

No matter how rigorous the evaluation, it can only ever be as good as the evidence provided. The aim of the second goal is to provide regulators with better evidence to underpin regulatory decisions, so that animals can gain more timely access to innovative treatments while they, the environment, and their keepers and wider human society are all protected from medicines whose benefits do not outweigh their risks.

Developers of medicines have the primary responsibility of generating the evidence needed to show their medicines are safe, effective and of suitable quality. However, regulators have a duty to outline clearly their expectations about the evidence they expect. Mismatches between the evidence expected and the evidence provided by developers are often the result of poor communication, especially in the early stages of development, and this can be exacerbated by inadequate data sharing between the relevant stakeholders. Increased collaboration in evidence generation and more open communication can obviously help and will be key to the development of new approaches to benefit-risk assessment during evaluation and pharmacovigilance after marketing. The core recommendations below aim to support this overall objective.

### Summary table

| Driving collaborative evidence generation - improving the scientific quality of evaluations |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                        | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Update Environmental Risk Assessments in line with the latest scientific knowledge          | <ul style="list-style-type: none"><li>▶ Contribute to the evaluation of novel approaches to ERA, and the EC considerations on the feasibility of establishing active substance monographs for all substances, including legacy active substances for which there is limited environmental information, providing input as required;</li><li>▶ Develop further guidance on when the use of persistent, bioaccumulative and toxic substances in animals can be justified;</li><li>▶ Develop additional guidance on the ERA of active substances used in aquaculture, including use of antimicrobials under the 'prescribing cascade';</li><li>▶ Cooperate with DG RTD to fund ERA-related research relevant to veterinary medicines, such as antimicrobial and antiparasitics resistance in the environment, and environmental effects of endocrine disruptors and contaminants (e.g. metals that co-select for antimicrobial resistance);</li><li>▶ Provide scientific support to the European Commission and the EU network to ensure that a "One Health" approach is applied to ERA;</li></ul> |

**Update Environmental Risk Assessments in line with the latest scientific knowledge**

- ▶ Increase cooperation in the field of ERA with European agencies, particularly ECHA, EFSA and EEA, and establish cooperation with international institutions, academic organisations and relevant initiatives;
- ▶ Strengthen capacity and capability to evaluate the environmental fate and effects of novel veterinary therapies, and to apply ERA to combinations of substances.

**Apply the latest scientific principles to the assessment of the safety of residues of veterinary medicines**

- ▶ Develop methodology to evaluate the consumer safety of biologically active substances for use in veterinary medicines for food producing animals;
- ▶ Engage with EU and international risk assessment bodies with a view to aligning methodology for estimating consumer exposure to residues, including dual-use substances;
- ▶ Engage with the EC's Directorate General Research and Innovation (DG RTD), other bodies and EU agencies to fund research relating to safety of residues;
- ▶ Work to increase capability in modelling, simulation and extrapolation (with applications in toxicological assessment, dose optimisation, environmental fate and residue depletion), for example, by seeking out and developing relevant training materials;
- ▶ Maintain awareness of developments in scientific thinking on cumulative or combined exposure to chemicals and reflect on relevance for the evaluation of safety of residues.

**Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance**

- ▶ Encourage increased stakeholder involvement in modernising veterinary pharmacovigilance and enhance international coordination;
- ▶ Using data on the sales of veterinary products, develop methodology to collate, analyse and communicate information about the incidence of adverse reactions related to medicines' use;
- ▶ Together with stakeholders, develop new and improved continuous surveillance and signal detection methodology using the network's pharmacovigilance database;
- ▶ Establish stakeholder expert groups for different food-producing species to access actual-use data of products in the field, both off and on label;
- ▶ Facilitate development of methodology using new technology, such as veterinary practice management systems and mobile phone apps, to increase reporting rates of adverse events.

**Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance**

- ▶ Improve communication of veterinary pharmacovigilance to the general public.

**Develop new and improved communication and engagement channels and methods to reach out to stakeholders**

- ▶ Address the need for improvement in product information content, including package leaflet layout and readability;
- ▶ Promote electronic formats of veterinary medicinal product information (veterinary ePI) that is readily and easily accessible and can be updated rapidly, making best use of new and digital technologies;
- ▶ Address the matter of under-reporting in veterinary pharmacovigilance using new communication tools and channels;
- ▶ Clearly inform the public of the scientific underpinning of new veterinary medicines and technologies, such as biological products including DNA vaccines or gene therapy;
- ▶ Ensure authoritative communication on key issues, particularly on issues where stakeholder concerns could be helped by better information;
- ▶ Promote better engagement with all stakeholders, especially those impacted by the CVMP opinions, i.e. animal owners.

**Develop new approaches to improve the benefit-risk assessment of veterinary medicinal products**

- ▶ Develop regulatory approaches to accommodate advances in technology such as whole genome sequencing and analytical methodology to access ever-lower limits of detection;
- ▶ Develop methodology for the benefit-risk evaluation of novel medicines intended to promote, or manage, the health of herds, besides the health of the individual animal;
- ▶ Promote systematic application of structured benefit-risk methodology and quality assurance systems in the approach to assessment and consistency of decision-making;
- ▶ Develop criteria to accept non-conventional sources of data (e.g. real-world evidence);
- ▶ Consider the regulatory framework and methodology to evaluate the efficacy of a veterinary medicine which is used to produce an improvement in human health, where benefit to the animal might be secondary;
- ▶ Optimise quality and consistency of outputs from EMA and maximise their dissemination to relevant stakeholders, especially for novel technologies.

### 4.2.1 Update Environmental Risk Assessments in line with the latest scientific knowledge

The Veterinary Medicines Regulation (EU) 2019/6 will require an evaluation by the European Commission of different approaches to strengthen environmental risk assessments (ERAs). This includes analysing the feasibility of establishing a monograph system for all substances, including legacy substances originally marketed before an ERA became mandatory. Given that there will be a short-term cost from establishing such information on active substances, the cost-benefit of establishing an active substance based assessment procedure will require careful consideration. Scientific developments that can be used to strengthen the existing ERA within the current methodology should be incorporated in relevant guidelines, ideally in close collaboration with EU and international partners. This is particularly relevant with respect to products used, for example, in aquaculture, and to antimicrobials and endocrine disrupting substances.

The Veterinary Medicines Regulation (EU) 2019/6 also includes provisions that aim to limit the use of persistent, bioaccumulative and toxic substances in veterinary medicinal products to be used in food-producing species, because of the potential dangers that the use of such substances may pose to the environment and to animal and public health. Unless there is evidence that the active substance is essential to prevent or control a serious risk to animal health, their use in food-producing animals will be prohibited. A review of existing guidance on what constitutes 'a serious risk to animal health' will be necessary and should be considered in the light of the WHO 'One Health' context.:

- ▶ Contribute to the evaluation of novel approaches to ERA, and the EC considerations on the feasibility of establishing active substance monographs for all substances, including legacy active substances for which there is limited environmental information, providing input as required;
- ▶ Develop further guidance on when the use of persistent, bioaccumulative and toxic substances in animals can be justified;
- ▶ Develop additional guidance on the ERA of active substances used in aquaculture, including

use of antimicrobials that can be used in food-producing aquatic species under the 'prescribing cascade';

- ▶ Cooperate with DG RTD to fund ERA-related research relevant to veterinary medicines, such as antimicrobial and antiparasitics resistance in the environment, and environmental effects of endocrine disruptors and contaminants;
- ▶ Provide scientific support to the European Commission and the EU network to ensure that a "One Health" approach is applied to ERA;
- ▶ Increase cooperation in the field of ERA with European agencies, particularly ECHA, EFSA and the European Environment Agency, and establish cooperation with international institutions, academic organisations and relevant initiatives;
- ▶ Strengthen capacity and capability to evaluate the environmental fate and effects of novel veterinary therapies, and to apply ERA to combinations of substances.

### 4.2.2 Apply the latest scientific principles to the assessment of the safety of residues of veterinary medicines

Maximum Residue Limits (MRL) are designed to ensure that consumers are not exposed to harmful levels of pharmacologically active substances via the diet. Pharmacologically active substances may not be included in veterinary medicinal products for use in food-producing animals unless the MRL status has been considered by the EMA's Committee for Veterinary Medicinal Products (CVMP) and established in line with Regulation (EC) 470/2009 and Commission Regulation (EU) 2018/782.

In the coming years, it is anticipated that the MRL framework will need to take account of novel biological active substances. Approaches to address potential consumer safety concerns resulting from exposure to their residues will also need to be developed. While biologicals that act as immunologicals (i.e. substances intended to produce active or passive immunity or to diagnose a state of immunity) are exempt from MRL requirements, other biological active substances are not. However, Regulation (EU) 2018/782 indicates that certain

biological active substances may not require a full MRL evaluation. EMA will develop guidance detailing the evaluation process to be carried out.

Pressure to align MRL setting methodology across different regulatory and regional frameworks will require evaluation of existing and alternative models for estimating consumer exposure to residues. This is because, in recent years there has been a divergence of approaches employed by EMA, EFSA and JECFA, with an associated risk of inconsistent evaluation outcomes, confusion for the public and divergent trade standards (MRLs).

A growing awareness of consumer exposure to chemicals from multiple sources requires further consideration of exposure to residues resulting from use of chemicals in multiple industrial sectors. While evaluation of consumer exposure to residues of veterinary medicines represents a standard workstream for EMA, improving modelling of combined exposure to residues of veterinary medicines and plant protection products requires further consideration. In a more general sense, the exposure of consumers to multiple chemicals is a growing area of interest and there is a need to remain abreast of developments in this area.

Finally, while developments in modelling and other technologies relevant to 3Rs is the subject of a separate recommendation, the development and implementation of relevant methodologies will require the commitment of experts from a range of disciplines and will have particular relevance in the field of safety testing.

- ▶ Develop methodology to evaluate the consumer safety of biologically active substances for use in veterinary medicines for food producing animals;
- ▶ Engage with EU and international risk assessment bodies with a view to aligning methodology for estimating consumer exposure to residues, including dual-use substances;
- ▶ Engage with the EC's Directorate General Research and Innovation (DG RTD), other bodies and EU agencies to fund research relating to safety of residues;
- ▶ Work to increase capability in modelling, simulation and extrapolation (with applications

in toxicological assessment, dose optimisation, environmental fate and residue depletion), for example, by seeking out and developing relevant training materials;

- ▶ Maintain awareness of developments in scientific thinking on cumulative or combined exposure to chemicals and reflect on relevance for the evaluation of safety of residues.

### **4.2.3 Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance**

Although the principles of human and veterinary pharmacovigilance, and the pharmacoepidemiological studies they support, are essentially the same, practice in the veterinary domain is often quite distinct. This difference has been recognised in the Veterinary Medicines Regulation (EU) 2019/6 which defines detailed and particular requirements for the operation of pharmacovigilance of veterinary medicinal products, including a move to continuous monitoring through means such as signal detection. This will require adaptation of EudraVigilance, the EU pharmacovigilance database system, to the requirements of the new veterinary legislation. In addition, as pharmacoepidemiology is relevant globally, and across multiple stakeholders, enhanced cooperation, training, harmonisation and improved communication is clearly required to elicit culture change in this area.

There is a well-recognised problem with under-reporting of suspected adverse effects in the veterinary domain, particularly with respect to food-producing animals. This situation has not yet improved despite increasing specialisation within the veterinary profession. There is a need to explore if and how use can be made of new digital technologies and communication channels (such as social media) in increasing reporting rates and improving communication of pharmacovigilance outputs to veterinary health professionals and the general public.

To work collaboratively with stakeholders and international partners to modernise veterinary pharmacoepidemiology and pharmacovigilance, EMA proposes to:



- ▶ Encourage increased stakeholder involvement in modernising veterinary pharmacovigilance and enhance international coordination;
- ▶ Using data on the sales of veterinary products, develop methodology to collate, analyse and communicate information about the incidence of adverse reactions related to medicines' use;
- ▶ Together with stakeholders, develop new and improved continuous surveillance and signal detection methodology using the network's pharmacovigilance database;
- ▶ Establish stakeholder expert groups for different food-producing species to access actual-use data of products in the field, both off and on label;
- ▶ Facilitate development of methodology using new technology, such as veterinary practice management systems and mobile phone apps, to increase reporting rates of adverse events;
- ▶ Improve communication of veterinary pharmacovigilance to the general public.

#### **4.2.4 Develop new and improved communication and engagement channels and methods to reach out to stakeholders**

The Agency has been engaging with its multiple stakeholders and issuing external communication since its inception. This two-way communication is critical to EMA's function as a regulator, and to the development of a culture of transparency. Communication around veterinary medicines is not as established as for human medicines and the need has been identified to increase public awareness of key outcomes with high importance for animal health as well as to give veterinary medicines more visibility. Such actions should also respond to a growing demand for transparency and information, aided by the growth of social media platforms and communication tools.

The need for communication tailored to the specific audience, be it veterinarians, SMEs, farmers or animal owners, is self-evident. This is particularly true when transferring knowledge about new technologies, for example. It is also relevant in the area of pharmacovigilance where social media may

be used as a channel to send reports of suspected side effects to veterinary medicines. The EU network must therefore continue to share best practice and ensure consistent approach to transparency and good communication. In addition, there is a need to improve how the product information for veterinary medicines is conveyed to users. The new veterinary legislation (Regulation (EU) 2019/6) provides for a package leaflet for authorised veterinary medicinal products to be available electronically. This is aligned with the recommendations issued in the EC report on current shortcomings in the summary of product characteristics and the package leaflet and how they could be improved in order to better meet the needs of patients and healthcare professionals, which includes an action to explore, in close liaison with stakeholders, how electronic means can be used to improve access to product information. While veterinary medicines are outside the scope of the EC report, progress on electronic product information (ePI) for human medicines will also be useful for any future activity for the product information of veterinary medicines.

- ▶ Address the need for improvement in product information content, including package leaflet layout and readability;
- ▶ Promote electronic formats of veterinary medicinal product information (veterinary ePI) that is readily and easily accessible and can be updated rapidly, making best use of new and digital technologies;
- ▶ Address the matter of under-reporting in veterinary pharmacovigilance using new communication tools and channels;
- ▶ Clearly inform the public of the scientific underpinning of new veterinary medicines and technologies, such as biological products including DNA vaccines or gene therapy;
- ▶ Enhance communication of the benefits, risks and uncertainties at the time of approval to improve decision making by prescribers/users;
- ▶ Ensure authoritative communication on key issues, particularly on issues where stakeholder concerns could be helped by better information;

- ▶ Promote better engagement with all stakeholders, especially those impacted by the CVMP opinions, i.e. animal owners.

#### **4.2.5 Develop new approaches to improve the benefit-risk assessment of veterinary medicinal products**

There is a continual need to adapt the European assessment of marketing authorisation applications to emerging science and technologies, be it in the area of innovative medicinal products, like stem cells and DNA vaccines, or the development of increasingly sensitive analytical technology such as molecular methods for detecting extraneous genetic material. It is important to balance the Agency's approach to innovative product development, and the application of new techniques, to ensure that appropriately informed and rigorous assessment is provided without creating unnecessary barriers to innovation or putting at risk animal and public health.

In the veterinary space, novel technology is enabling the development of products that both facilitate improved animal health outcomes and increase animal productivity. However, these create new challenges with respect to the benefit-risk evaluation, as an example, the advantages might be to the animal keepers rather than the animals, and there is considerable public resistance to introduction of technologies that bring risk but no benefits to the recipient animals themselves. New regulatory approaches will therefore be required for such borderline cases where it is not clear if the indications qualify the products as VMPs.

It will also be important to communicate clearly and transparently about the decisions taken, optimising the scientific quality and consistency of Agency outputs and maximising dissemination and impact of the communication of these outputs once finalised.

EMA therefore proposes to:

- ▶ Develop regulatory approaches to accommodate advances in technology such as whole genome sequencing and analytical methodology to access ever-lower limits of detection;
- ▶ Develop methodology for the benefit-risk evaluation of novel medicines intended to

promote, or manage, the health of herds, besides the health of the individual animal;

- ▶ Promote systematic application of structured benefit-risk methodology and quality assurance systems in the approach to assessment and consistency of decision-making;
- ▶ Develop criteria to accept non-conventional sources of data (e.g. real-world evidence);
- ▶ Consider the regulatory framework and methodology to evaluate the efficacy of a veterinary medicine which is used to produce an improvement in human health, where benefit to the animal might be secondary;
- ▶ Optimise quality and consistency of outputs from EMA and maximise their dissemination to relevant stakeholders, especially for novel technologies.

### 4.3 Goal 3: Addressing emerging health threats and availability/therapeutic challenges

The core mission of all regulatory bodies dealing with medicinal products is to protect human and animal health. The aim of the third goal is to ensure that the regulatory system can respond effectively to address the need for treatments of emerging health threats, and the availability of medicines for existing ones. With human health invariably taking priority, animal health, for which available treatments are more limited, is at greater risk of compromise during emerging health threats. Therefore, the need to ensure the availability of existing and novel medicines is of upmost importance.

In support of this goal, recommendations have been made in several areas. Antimicrobial and antiparasitic agent resistance are areas of particular importance to address so as to ensure the availability of treatments, and there is a need to support the development of veterinary vaccines, not only as an alternative to antimicrobials but as a tool to prevent and manage the emergence of zoonoses that threaten human health.

The EMA's experience to date in addressing emerging health threats has shown the importance of cooperation and data-sharing on a global level in achieving success in this area. It has also highlighted the need for proportionate flexibility in the application of regulatory science to counter the impact of a potentially rapidly emerging health threat.

#### Summary table

| Addressing emerging health threats and availability/therapeutic challenges       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                             | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Continue to promote the responsible use of antimicrobials and their alternatives | <ul style="list-style-type: none"><li>▶ Work in partnership with EC, other EU Agencies and regulators and international bodies to promote the responsible use of antimicrobials and their alternatives;</li><li>▶ Enhance the promotion of the responsible use of antimicrobials via updated and/or new regulatory guidance and scientific opinion;</li><li>▶ Develop a regulatory approach/framework to promote alternatives to conventional antimicrobials and novel paradigms;</li><li>▶ Explore the possibility of new funding models to generate data to support existing authorised products and to incentivise new product development;</li><li>▶ Provide scientific and regulatory support to encourage development of veterinary antimicrobials and alternatives, to fill therapeutic gaps, without adversely impacting public health;</li><li>▶ Foster development of rapid pen-side diagnostics to support responsible use.</li></ul> |

|                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Coordinate network activities to improve data collection on antimicrobial use in animals</b> | <ul style="list-style-type: none"> <li>▶ Define requirements for harmonised sales and use data collection for antimicrobial medicinal products used in animals;</li> <li>▶ Adjust the methodology for analysis of antimicrobial data, by considering approaches developed internationally;</li> <li>▶ Develop methodology to collate, analyse and communicate data on antimicrobial use per species;</li> <li>▶ Inform policy decisions via enhanced cooperation with European institutions (EFSA, ECDC) to collate data on antimicrobial use with information on AMR in animals, humans and food;</li> <li>▶ Participate in international initiatives to reduce the risk of AMR.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Engage with stakeholders to minimise the risks of antiparasitic resistance</b>               | <ul style="list-style-type: none"> <li>▶ Cooperate with other EU agencies / bodies on initiatives concerning antiparasitic resistance, e.g. the EC's Directorate General – Research and Innovation (DG RTD) on research into reliable tests to detect or measure resistance, or monitoring of antiparasitic use or resistance in food-producing species and non-food producing animals;</li> <li>▶ Participate actively in international initiatives that aim to develop strategies to combat antiparasitic resistance and to establish best practices on the use of veterinary antiparasitic medicines;</li> <li>▶ Promote responsible use of antiparasitics in the EU.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Promote and support development of veterinary vaccines</b>                                   | <ul style="list-style-type: none"> <li>▶ Interact collaboratively with industry and other stakeholders to focus development on areas where vaccines are most needed;</li> <li>▶ Acknowledge that different benefit-risk approaches are required for assessment of specific vaccine types (e.g. vaccines for zoonotic diseases, limited markets, exceptional circumstances);</li> <li>▶ Develop a regulatory framework for authorisation, under exceptional circumstances, of vaccines for emerging health threats and benefit-risk monitoring post-approval;</li> <li>▶ Clarify when field efficacy trials to support marketing authorisation applications for new vaccines could be omitted;</li> <li>▶ Explore feasibility of establishing a framework for using epidemiological modelling data to support the demonstration of vaccine efficacy;</li> <li>▶ Develop appropriate and proportionate guidance to maximise opportunities offered by Regulation (EU) 2019/6 for promoting availability of vaccines (vaccine antigen master files, vaccine platform technology master files and multi-strain dossiers);</li> </ul> |

**Promote and support development of veterinary vaccines**

- ▶ Advance understanding of the science behind novel technologies to ensure appropriate regulatory oversight and foster ability to exploit added value of new technologies.

### **4.3.1 Continue to promote the responsible use of antimicrobials and their alternatives**

Responding to the ever-increasing public health threat of antimicrobial resistance (AMR) demands a 'One Health' approach and the Agency is fully committed to supporting the European Commission action plan on AMR. On the veterinary side, the CVMP has had a strategy on antimicrobials in place since 1999. The ban on the use of antibiotics as growth promoters was finally completed within the EU in 2006 and all antibiotics for veterinary use are now available only on prescription although quantities used vary substantially between countries. In addition, EMA and EFSA have together reviewed the measures that have been taken to reduce the use of antimicrobials in animal husbandry in the EU and published a battery of recommendations to promote prudent use from the national level down to the farmer.

The new regulation for veterinary medicines will introduce a 'toolbox' of measures to improve control of antimicrobial use in veterinary practice, including the creation of a list of antimicrobial substances whose use would be restricted to humans. The Agency anticipates providing input in this area, to supplement ongoing work including the implementation of the CVMP's strategy on antimicrobials and measures to limit the effects of AMR. It will also continue to develop EU and international cooperation on AMR.

Measures will be needed for maintaining availability of existing antimicrobials, which may include finding novel approaches to model or extrapolate data so that old but important antimicrobials can meet updated requirements and be kept on the market. In addition, regulatory support should be given to promote the development of novel antimicrobials, or alternatives which could reduce antimicrobial use such as immunostimulants. The Agency therefore proposes to:

- ▶ Work in partnership with EC, other EU Agencies and regulators and international bodies to

promote the responsible use of antimicrobials and their alternatives;

- ▶ Enhance the promotion of the responsible use of antimicrobials via updated and/or new regulatory guidance and scientific opinion;
- ▶ Develop a regulatory approach/framework to promote alternatives to conventional antimicrobials and novel paradigms;
- ▶ Explore the possibility of new funding models to generate data to support existing authorised products and to incentivise new product development;
- ▶ Provide scientific and regulatory support to encourage development of veterinary antimicrobials and alternatives, to fill therapeutic gaps, without adversely impacting public health;
- ▶ Foster development of rapid pen-side diagnostics to support responsible use.

### **4.3.2 Coordinate network activities to improve data collection on antimicrobial use in animals**

The EMA, in collaboration with participating European countries, analyses and reports antimicrobial consumption data that are collected and submitted to the ESVAC project. This data provides background information for actions to counter antimicrobial resistance and to achieve the responsible and reduced use of antimicrobials in animals. Inter-agency reports relating to antimicrobial consumption and resistance are also being produced with increasingly in-depth analyses.

The new veterinary legislation foresees that in addition to harmonised and standardised data submission, the quality of the data will be enhanced. Certain data requirements will need to be defined and should take account of those developed internationally. In addition, the development of improved methodologies to analyse exposure and

use of antimicrobials in different animal species is required.

- ▶ Define requirements for harmonised sales and use data collection for antimicrobial medicinal products used in animals;
- ▶ Adjust the methodology for analysis of antimicrobial data, by considering approaches developed internationally;
- ▶ Develop methodology to collate, analyse and communicate data on antimicrobial use per species;
- ▶ Inform policy decisions via enhanced cooperation with European institutions (EFSA, ECDC) to collate data on antimicrobial use with information on AMR in animals, humans and food;
- ▶ Participate in international initiatives to reduce the risk of AMR.

#### **4.3.3 Engage with stakeholders to minimise the risks of antiparasitic resistance**

Antiparasitic veterinary medicines are widely used to treat and prevent parasitic diseases in production and companion animals; however, a significant number of these parasites might also have zoonotic potential (e.g., echinococcosis), or can act as a vector for other diseases (e.g. leishmaniosis, Lyme disease). As a consequence of climate changes and an increase in the movement of animals, new parasite species and diseases carried by parasite vectors are spreading across the EU into hitherto non-endemic regions. This comes along with changes in animal husbandry systems, which have resulted in increased use of antiparasitic substances in animals.

With an increased (routine) use of antiparasitic substances, concern has been raised about an increase in the development of resistance in parasites and a possible consequential lack of appropriate therapeutic alternatives. Resistance has so far mostly been reported for certain classes of antiparasitics (e.g. anthelmintics) and target species (e.g. sheep, horses), but a future increase to other classes/species cannot be excluded.

Various approaches have been suggested to delay the development of antiparasitic resistance and to ensure the availability of effective veterinary antiparasitic medicines, including the development of new veterinary medicinal products, changes in the way antiparasitic medicines are used in animals (e.g. taking account of the principle of “refugia”), but also new strategies in animal husbandry. However, unlike the situation for antimicrobials, there remain significant knowledge gaps in the understanding of resistance development across antiparasitic classes and target species. There is no (routine) EU-wide data monitoring system, as well as an absence of detailed knowledge about other methods on how to delay or prevent resistance development (e.g. herd/pasture management). There is thus a need for international cooperation to fill these gaps and the Agency proposes to:

- ▶ Cooperate with other EU agencies / bodies on initiatives concerning antiparasitic resistance, e.g. the EC’s Directorate General – Research and Innovation (DG RTD) on research into reliable tests to detect or measure resistance, or monitoring of antiparasitic use or resistance in food-producing species and non-food producing animals;
- ▶ Participate actively in international initiatives that aim to develop strategies to combat antiparasitic resistance and to establish best practices on the use of veterinary antiparasitic medicines;
- ▶ Promote responsible use of antiparasitics in the EU.

#### **4.3.4 Promote and support development of veterinary vaccines**

Vaccination is one of the most effective tools for preventing animal diseases and for promoting animal health and welfare, safe food production and public health. Despite their importance, there are often challenges in ensuring that suitable veterinary vaccines are available in a timely manner.

Veterinary vaccines as well as veterinary biologicals that take advantage of the opportunities arising from innovative biotechnology form an increasing proportion of the authorisation applications submitted to the Agency. They offer an opportunity to overcome problems such as a shortage in the pipeline of novel

pharmaceutically active molecules and increasing public concern about the safety of residues in foodstuffs of animal origin, and a potential route to reducing the use of antimicrobials.

In order to further promote and support the authorisation of veterinary vaccines, the following actions are proposed:

- ▶ Interact collaboratively with industry and other stakeholders to focus development on areas where vaccines are most needed;
- ▶ Acknowledge that different benefit-risk approaches are required for assessment of specific vaccine types (e.g. vaccines for zoonotic diseases, limited markets, exceptional circumstances);
- ▶ Develop a regulatory framework for authorisation, under exceptional circumstances, of vaccines for emerging health threats and benefit-risk monitoring post-approval;
- ▶ Clarify when field efficacy trials to support marketing authorisation applications for new vaccines could be omitted;
- ▶ Explore feasibility of establishing a framework for using epidemiological modelling data to support the demonstration of vaccine efficacy;
- ▶ Develop appropriate and proportionate guidance to maximise opportunities offered by Regulation (EU) 2019/6 for promoting availability of vaccines (vaccine antigen master files, vaccine platform technology master files and multi-strain dossiers);
- ▶ Advance understanding of the science behind novel technologies to ensure appropriate regulatory oversight and foster ability to exploit added value of new technologies.



## 4.4 Goal 4: Enabling and leveraging research and innovation in regulatory science

The Agency’s final goal in the veterinary, as in the human, sphere is to develop the existing interaction between the EU regulatory network and academia further, in order to be kept informed of relevant scientific innovations and research and anticipate solutions to regulatory needs and challenges. This is the key to delivering the other strategic goals and recommendations laid out in this document.

It is envisaged that this aim will be achieved by establishing a novel regulatory science and innovation platform in partnership with academic research centres. The ultimate aim is to ensure that regulatory science remains at the cutting edge so that EMA can deliver its fundamental mission of protecting human and animal health and facilitating the availability of medicines to animals.

### Summary table

| Enabling and leveraging research and innovation in regulatory science                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Core recommendations                                                                                                           | Underlying actions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science | <ul style="list-style-type: none"><li>▶ Develop and implement a roadmap that clarifies where and how partnerships with academia can best contribute to the human and veterinary RSS. This should build on existing networks and consider how best to support academics developing medicines while identifying practical actions that facilitate interaction at strategic, tactical and operational level;</li><li>▶ Identify, in consultation with research institutions, academia and other relevant stakeholders, fundamental research and associated training/ education topics in strategic areas of regulatory science;</li><li>▶ Proactively engage with DG Research &amp; Innovation, DG-SANTE, the Innovative Health Initiative, the ENVI Agencies and Member State funding agencies to propose and issue calls to establish research collaborations;</li><li>▶ Evaluate the conduct, results and impact of imposed and voluntary post authorisation safety studies;</li><li>▶ Systematically conduct impact research following major regulatory action where additional risk minimisation measures are introduced. Such research should include both quantitative and qualitative approaches.</li></ul> |

**Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions**

- ▶ Ring-fence EMA funding to address rapidly emerging regulatory science research questions;
- ▶ Ensure close interaction between network scientists, academia and learned societies to deliver tangible impact through translation of this applied research into new drug products and regulatory tools;
- ▶ Actively engage, through these applied projects, in training early-career researchers in regulatory science (e.g., via placements within the network);
- ▶ Create a bridging action plan to feed iterative and interactive engagements between these stakeholders as a core strategy of the EMA, National (HMA and EU-IN) and global (ICMRA) regulatory authorities.

**Identify and enable access to the best expertise across Europe and internationally**

- ▶ Explore the creation of a 'shared environment' in which novel insights and experiences are shared among all stakeholders, including innovator and generic (complex) drug manufacturers, regulatory bodies and academia;
- ▶ Propose a framework that allows for adequate identification and involvement of independent experts and ensures a rigorous conflicts of interest policy;
- ▶ Develop a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle.

**Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders**

- ▶ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient;
- ▶ Collaborate with the EMRN to:
  - » Identify gaps in training and learning objectives;
  - » Work with academic institutions to build and provide regulatory training modules or courses;
- ▶ Conduct horizon scanning in key areas of innovation via collaborations with academia, the EU-Innovation Network and ICMRA;
- ▶ Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders.

**4.4.1 Develop network-led partnerships with academic/research centres to undertake research in strategic areas of regulatory science**

Life sciences research, much of which is relevant to medicines development, is strong in the EU. To enhance its impact, increased dialogue between scientists and regulatory authorities is crucial. With this in mind, more regular, iterative engagement will be developed between regulators, funders, and research centres in order to develop partnerships for research in selected areas of regulatory science.

The aim is to provide a mechanism for scientists in the regulatory network and research centres to collaborate in identifying and tackling important research questions. Such collaboration will ensure a coordinated approach across the EU network, so that regulatory decision-making and policy can be evidence-driven and consistent.

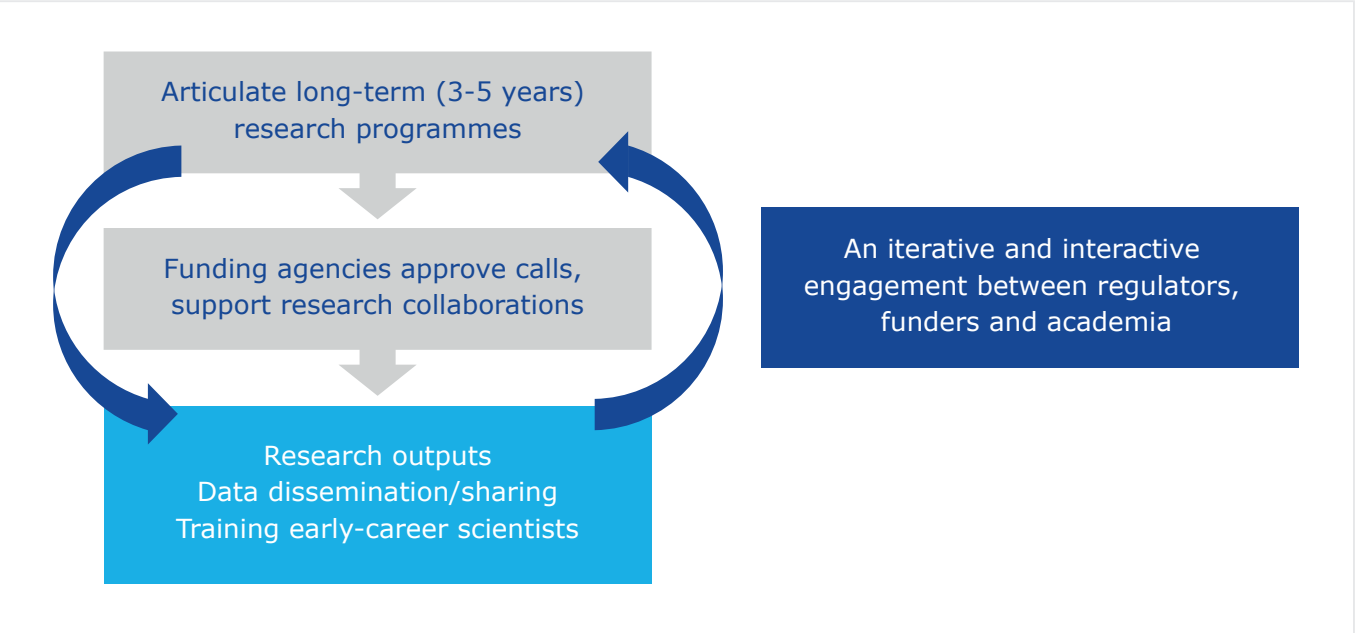
The Agency proposes the following actions:

- ▶ Develop and implement a roadmap that clarifies where and how partnerships with academia can best contribute to the human and veterinary

RSS. This should build on existing networks and consider how best to support academics developing medicines while identifying practical actions that facilitate interaction at strategic, tactical and operational level;

- ▶ Identify, in consultation with research institutions, academia and other relevant stakeholders, fundamental research and associated training/education topics in strategic areas of regulatory science;
- ▶ Proactively engage with DG Research & Innovation, DG-SANTE, the Innovative Health Initiative, the ENVI Agencies and Member State funding agencies to propose and issue calls to establish research collaborations;
- ▶ Evaluate the conduct, results and impact of imposed and voluntary post authorisation safety studies;
- ▶ Systematically conduct impact research following major regulatory action where additional risk minimisation measures are introduced. Such research should include both quantitative and qualitative approaches.

**Figure 11.** Network-led partnerships with academia to undertake research in strategic areas of regulatory science



#### 4.4.2 Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

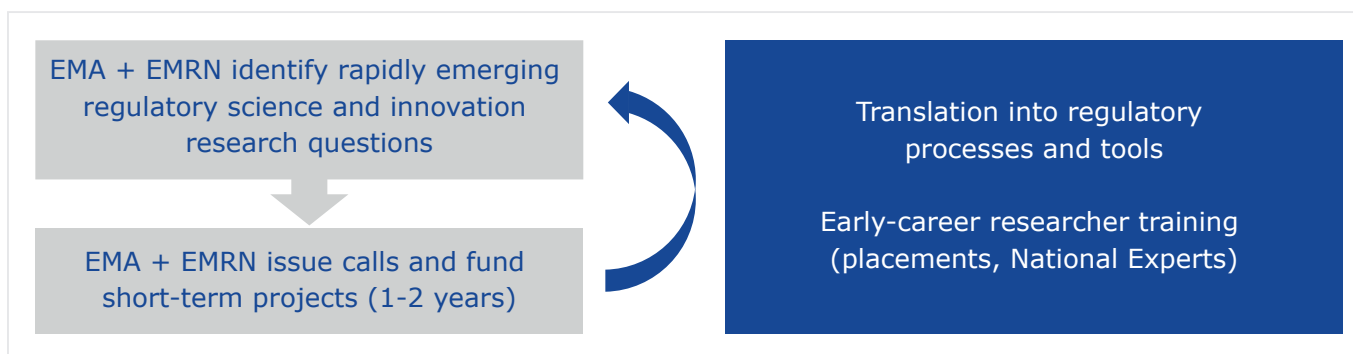
The collaboration in regulatory science above represents a platform that can also be applied to address, in a timely way, emerging innovations that require new regulatory competencies, methods, or tools.

The aim is to allow network scientists and academia to collaborate in exploring specific, evolving regulatory questions in order to develop the skills and tools that the network needs to respond. Resource capacity will need to be reserved to allow this.

To leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions, the Agency proposes to implement the following actions:

- ▶ Ring-fence EMA funding to address rapidly emerging regulatory science research questions;
- ▶ Ensure close interaction between network scientists, academia and learned societies to deliver tangible impact through translation of this applied research into new drug products and regulatory tools;
- ▶ Actively engage, through these applied projects, in training early-career researchers in regulatory science (e.g., via placements within the network);
- ▶ Create a bridging action plan to feed iterative and interactive engagements between these stakeholders as a core strategy of the EMA, National (HMA and EU-IN) and global (ICMRA) regulatory authorities.

**Figure 12.** Collaboration between academia and network scientists to address rapidly emerging regulatory science research questions



#### 4.4.3 Identify and enable access to the best expertise across Europe and internationally

Understandably, the top experts in any field are in high demand as invited speakers at international meetings, as reviewers of grant applications and peer-reviewed journal publications, and as consultants to industry. Regulators too require access to the highest levels of expertise, and as scientific disciplines become ever more refined, this means competing for the skills and knowledge of a relatively small number of people.

The partnerships envisaged between the network and academia will naturally need to seek the best international expertise in key areas of regulatory science. It is essential, therefore, that access to such expertise be facilitated, by adopting a proportionate approach to potential conflicts of interest, to permit the best advice to be accessed in areas of innovation that are new to regulators and are becoming ever more specialised.

In order to implement this recommendation, the Agency proposes to do the following:

- ▶ Explore the creation of a 'shared environment' in which novel insights and experiences are shared

among all stakeholders, including innovator and generic (complex) drug manufacturers, regulatory bodies and academia;

- ▶ Propose a framework that allows for adequate identification and involvement of independent experts and ensures a rigorous conflicts of interest policy;
- ▶ Develop a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle.

» Work with academic institutions to build and provide regulatory training modules or courses;

- ▶ Conduct horizon scanning in key areas of innovation via collaborations with academia, the EU-Innovation Network and ICMRA;
- ▶ Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders.

#### **4.4.4 Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders**

The open exchange of knowledge is fundamental to science and a driver of progress. Such exchange, via a close partnership between the regulatory network and the expertise available in universities and research institutes, offers important benefits to both partners.

The development of high-quality learning materials in those basic and applied biomedical sciences that make up regulatory science (i) will benefit the training needs of the network while (ii) at the same time improving the knowledge of academic groups and scientists working in the field of health research, thus enhancing the success and outcomes of academia driven clinical research and (iii) strengthening long term knowledge (about medicines development and regulatory science) during professional education and training at both undergraduate and postgraduate levels.

In order to implement this recommendation, the Agency proposes to do the following:

- ▶ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient:
- ▶ Collaborate with the EMRN to:
  - » Identify gaps in training and learning objectives;



## 5. Working together: international regulatory science cooperation

Cooperation with regulators outside the EU network is key to much of the vision outlined in the strategy. This cooperation is mandated by the globalisation of medicine: in its supply chains, its research and development and its expertise. International cooperation in dealing with the common challenges posed by innovation helps solve these complexities through joint problem solving, resource pooling, capacity building and the convergence of regulatory tools and standards. EMA's experience of working within a network means it is well placed to offer leadership in building mutual reliance and cooperation. Although multilateral cooperation does require resources, promoting reliance and work-sharing with other regulators is ultimately an investment in more efficient resource use, for all parties.

To achieve, in particular, supply chain and data integrity, EMA seeks to share data and harmonise standards in many areas of the medicine lifecycle, including good manufacturing practice (GMP) and good clinical practice (GCP), innovation in clinical trials, scientific advice and pharmacovigilance. Cooperation in GMP/GCP goes beyond recognising each other's inspections or data sharing, and includes the involvement of local authorities in inspections to strengthen mutual understanding and build capacity. This cooperation occurs predominantly with PIC/S, FDA, MHLW/PMDA, Health Canada and WHO but

also with many others across human and veterinary medicine.

Additionally, EMA is building capacity internationally by involving WHO and non-EU regulators in, for example, initiatives to support training, or to address specific public health priorities such as infectious disease outbreaks, shortages of medicinal products or AMR. It also aims to ensure harmonised communication on key issues such as unfounded scares.

Reliance, where an authority relies on work done by another authority but retains its full power of decision, will continue to be supported by EMA across various initiatives. EU-Medicines for All (EU\_M4all), under article 58, allows access to innovative medicines in Low- and Middle-Income Countries (LMIC) based on CHMP opinions. The impact of such opinions is notable with 138 approvals in 90 countries worldwide, and EMA will encourage application by non-traditional sponsors such as NGOs. EMA will develop its support to the Collaborative Registration Procedure and share Assessment Reports to speed up approvals in LMICs. Through reliance, EMA can support best practices and better use of international standards. Reliance will facilitate the use of science-based approaches for emerging regulatory challenges

such as medicinal products shortages, AMR and outbreaks of infectious diseases.

EMA will therefore pursue a continued deepening of international cooperation with a focus on horizon scanning and science-based innovation. Nearly all the topics considered in this strategy are relevant to other regulators, who share these challenges, and exchanging views on how to tackle them and to adapt is mutually beneficial. This should be pursued through all of the channels currently opened between regulators ranging from high level fora such as ICH, ICMRA, ICDRA as well as more specialist focus channels such as the range of cluster meetings with which the Agency is involved.

In the veterinary domain international cooperation occurs mainly through established forums such as CODEX, OIE, VICH and its Outreach Forum. Recently a proposal has been made to explore the creation of an international coalition of regulatory agencies for veterinary medicines. EMA is supportive of this concept and will participate to evaluate the benefits that such a coalition could bring in areas such as training, capacity building and aligning approaches to the regulation of novel veterinary therapies.



## 6. List of acronyms

|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| <b>AI</b>       | Artificial Intelligence                                                       |
| <b>AMR</b>      | Antimicrobial Resistance                                                      |
| <b>ATMP</b>     | Advanced Therapy Medicinal Product                                            |
| <b>BR</b>       | Benefit-risk                                                                  |
| <b>CODEX</b>    | Codex Alimentarius                                                            |
| <b>CQA</b>      | Critical Quality Attribute                                                    |
| <b>CVMP</b>     | Committee for Veterinary Medicinal Products (EMA)                             |
| <b>DG RTD</b>   | European Commission Directorate General for Research and Innovation           |
| <b>DG AGRI</b>  | European Commission Directorate General for Agriculture and Rural Development |
| <b>DG JRC</b>   | European Commission Directorate General Joint Research Centre                 |
| <b>DG SANTE</b> | European Commission Directorate General for Health and Food Safety            |
| <b>EC</b>       | European Commission                                                           |
| <b>ECHA</b>     | European Chemicals Agency                                                     |
| <b>EEA</b>      | European Economic Area                                                        |
| <b>EFSA</b>     | European Food Safety Authority                                                |
| <b>EMA</b>      | European Medicines Agency                                                     |
| <b>EMRN</b>     | European Medicines Regulatory Network, the EU network                         |
| <b>ePI</b>      | electronic Product Information                                                |
| <b>ERA</b>      | Environmental Risk Assessment                                                 |
| <b>FDA</b>      | Food and Drug Administration (USA)                                            |
| <b>FIM</b>      | First-In-Man                                                                  |
| <b>GCP</b>      | Good Clinical Practice                                                        |
| <b>GMP</b>      | Good Manufacturing Practice                                                   |
| <b>HMA</b>      | Heads of Medicine Agencies                                                    |
| <b>HTA</b>      | Health Technology Assessment body                                             |
| <b>ICDRA</b>    | International Coalition of Drug Regulatory Authorities                        |

|                |                                                                                                                       |
|----------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>ICH</b>     | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| <b>ICMRA</b>   | International Coalition of Medicines Regulatory Authorities                                                           |
| <b>IMI</b>     | Innovative Medicines Initiative                                                                                       |
| <b>IVDR</b>    | EU In Vitro Diagnostic Regulation (2017/746)                                                                          |
| <b>JEFCA</b>   | Joint FAO/WHO Expert Committee on Food Additives                                                                      |
| <b>MAA</b>     | Marketing Authorisation Application                                                                                   |
| <b>MDR</b>     | EU Medical Device Regulation (2017/745)                                                                               |
| <b>MRL</b>     | Maximum Residue Limit                                                                                                 |
| <b>NAMs</b>    | New Approach Methodologies                                                                                            |
| <b>NITAG</b>   | National Immunisation Technical Advisory Group                                                                        |
| <b>OECD</b>    | Organisation for Economic Co-operation and Development                                                                |
| <b>OIE</b>     | World Organisation for Animal Health                                                                                  |
| <b>PI</b>      | Product Information                                                                                                   |
| <b>PIC/S</b>   | Pharmaceutical Inspection Collaboration Scheme                                                                        |
| <b>PK/PD</b>   | Pharmacokinetics/Pharmacodynamics                                                                                     |
| <b>PMDA</b>    | Pharmaceuticals and Medical Devices Agency (Japan)                                                                    |
| <b>PRIME</b>   | Priority Medicines Scheme                                                                                             |
| <b>PRO</b>     | Patient-Reported Outcome                                                                                              |
| <b>PROM</b>    | Patient-Reported Outcome Measure                                                                                      |
| <b>RWD</b>     | Real World Data                                                                                                       |
| <b>SciCoBo</b> | Scientific Coordination Board                                                                                         |
| <b>SEND</b>    | Standard for Exchange of Nonclinical Data                                                                             |
| <b>SME</b>     | Small or Medium-sized Enterprise                                                                                      |
| <b>STAMP</b>   | Commission Group on Safe and Timely Access to Medicines for Patients                                                  |
| <b>VICH</b>    | Veterinary International Conference on Harmonization                                                                  |
| <b>WHO</b>     | World Health Organization                                                                                             |



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