EUROPEAN MEDICINES AGENCY

SCIENCE MEDICINES HEALTH

Draft EMA Regulatory Science to 2025

Strategic reflection

Contents

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 these emerging science and technological innovations? E.g., big data, precision medicine, novel manufacturing, novel clinical trials design, 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 have asked the Chairs of the Scientific Committees to reflect upon these questions and propose our future regulatory science strategy, which we now seek to enrich by consulting with our key stakeholders.

While we must absorb the disruption resulting from Brexit through 2019, the European network needs to prepare for the 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 New Veterinary Regulation (NVR) over the coming years. However, we also must look beyond the NVR 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 will be a key element within the next European Regulatory Network Strategy to 2025, which will be developed together with the Member States and the European Commission. 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. The launch of this stakeholder consultation provides an opportunity for you to help shape the Agency's regulatory science strategy and decide where the future priorities and resources should be attributed.

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	
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 ▸ 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

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)
	▸ 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
	▸ Promote global cooperation to anticipate and address supply problems
	▸ 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 academia to undertake fundamental research in strategic areas of regulatory science
	▸ Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions
	▸ 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	
1. Catalysing the integration of science and technology in drug development	▸ Transform the regulatory framework for innovative veterinary medicines ▸ Reinforce and further embed application of the 3Rs principles ▸ Facilitate implementation of novel manufacturing models
2. Driving collaborative evidence generation and improving the scientific quality of evaluations	▸ Update Environmental Risk Assessments in line with the latest scientific knowledge ▸ Apply the latest scientific principles to the assessment of the safety of residues of veterinary medicines ▸ Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance ▸ Develop new and improved communication and engagement channels and methods to reach out to stakeholders ▸ Develop new approaches to improve the benefit-risk assessment of veterinary medicinal products
3. Addressing emerging health threats and availability/ therapeutic challenges	▸ Continue to promote the responsible use of antimicrobials and their alternatives ▸ Coordinate Network activities to improve data collection on antimicrobial use in animals ▸ Engage with stakeholders to minimise the risks of antiparasitic resistance ▸ Promote and support development of veterinary vaccines
4. Enabling and leveraging research and innovation in regulatory science	▸ Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science ▸ Leverage collaborations between academia and network scientists to address rapidly emerging regulatory science research questions ▸ 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

1. Introduction-the regulatory framework

The European regulatory system for medicines (the 'EU network') 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 500 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."

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.

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 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.

2. A strategic reflection

This strategic reflection document 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 in light of upcoming 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 are now being published for public consultation so that the input of our many stakeholders can be sought.

Following the consultation period, the final versions of these recommendations and actions will be published, along with the comments received. Prioritisation and measurable outcomes for each core recommendation and underlying action will be established following stakeholder input. This will be agreed for implementation and will be translated into detailed initiatives and embedded into work plans for EMA and its scientific committees via the EU Network 2025 Strategy.

The reflection and consultation is therefore an opportunity for regulators and our stakeholders jointly to shape a vision for regulatory science that will in turn feed into the wider EU network strategy in the period 2020-25.

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 referendum on membership of 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 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 have now been distilled into this strategic reflection document, which is being presented for public consultation to allow the wider stakeholder community to have its say.

Seeking the views of stakeholders

The purpose of the public consultation is to seek the widest possible views on whether the proposals will address the need to engage with regulatory science as it evolves through to 2025 and beyond. By highlighting where the need is greatest, stakeholders have the opportunity to guide the future strategic application of financial and human resources to address these needs.

The views being sought on the strategic reflection are both general and specific: on the extent and nature of the broader goals and recommendations and on the individual actions that must be taken to address them.

Do stakeholders consider the goals appropriate? Are the core recommendations and proposed actions the right way to support them and how might they be approached? Are significant elements missing? The programme of actions is extensive: thus, stakeholder views on which areas require the most urgent prioritisation, or which, in contrast, are less of a priority for particular stakeholder groups, will in particular be a welcome contribution to future planning.

A public health aim

The reflection on potential areas of regulatory science engagement described in these documents recognises first and foremost that science, technology and information (quantity, handling, dissemination) are changing society in general, and medicinal product development in particular, at a fast pace, and regulators must keep up.

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 public health and provide European citizens with optimal medicines regulation in the coming years.

3. Human medicines-five strategic goals for regulatory science

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, five strategic goals are proposed. Each is associated with a set of core recommendations and their supporting actions. Stakeholder input is sought in refining, developing and prioritising these.

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

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 safe, 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 regulatory process, EMA is proposing the core recommendations outlined below.

Summary table

Catalysing the integration of science & technology in drug development	
Core recommendations	*Underlying actions*
Support developments in precision medicine, biomarkers and 'omics	▸ Enhance early engagement with novel biomarker developers to facilitate regulatory qualification; ▸ 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.
Support translation of advanced therapy medicinal products (ATMPs) into patient treatments	▸ Identify therapies that address unmet medical need; ▸ Provide assistance with early planning, method development and clinical evaluation; ▸ Support evidence generation, pertinent to downstream decision-makers; ▸ Address the challenges of decentralised ATMP manufacturing and delivery locations; ▸ Raise global awareness of ATMPs to maximise knowledge sharing, promote data collection.
Promote and invest in the PRIME scheme	▸ Invest in external communication to better explain and promote PRIME; ▸ Evaluate current capacity and identify areas for increased investment; ▸ Shorten the time between scientific advice, clinical trials and MAA submission; ▸ Collaborate with stakeholders to ensure efficient oversight post-approval; ▸ Leverage collaboration with patients, healthcare professionals, academia and international partners.
Facilitate the implementation of novel manufacturing technologies	▸ Recruit expertise in novel manufacturing technologies to enhance the assessment process; ▸ Identify bottlenecks and propose modernisation of relevant regulations to facilitate novel manufacturing; ▸ Address regulatory challenges in point-of-care manufacturing, e.g. concept of batch control, role of the Qualified Person;Facilitate a flexible approach in application of Good Manufacturing Practice.

Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products	▸ Define how benefit-risk of borderline products is assessed and communicated;
	▸ Enrich expertise at the interface between medicines, medical devices and borderline products;
	▸ Facilitate the regulatory pathway between notified bodies and medicines' regulators;
	▸ Gain insight in innovation on drug-device combination products via horizon scanning.
Develop understanding of, and regulatory response to, nanotechnology and new materials in pharmaceuticals	▸ Raise awareness of new nanomedicines and materials via the EU-Innovation Network;
	▸ Generate guidance addressing PK/PD requirements and long-term efficacy and safety;
	▸ Develop guidance on regulatory pathways with device regulators and notified bodies.
Diversify and integrate the provision of regulatory advice along the development continuum	▸ Promote more integrated medicines development aligning scientific advice, clinical trials approval and Good Clinical Practice oversight;
	▸ Create complementary and flexible advice mechanisms to support innovative product development expanding multi-stakeholder consultation platforms;
	▸ 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, either to stratified populations (biomarker-led medicine) or different stages of the disease, or 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 actions proposed by EMA to support this recommendation are:

▸ Enhance early engagement with novel biomarker developers to facilitate regulatory qualification;

▸ 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.

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 also 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 current challenges and those that will rise 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;

‣ Support evidence generation, pertinent to downstream decision-makers;

‣ Address the challenges of decentralised ATMP manufacturing and delivery locations;

‣ Raise global awareness of ATMPs to maximise knowledge sharing, promote data collection.

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 not only in the regulatory system but also in the clinical care system to support extensive monitoring of post-licensing evidence generation. Involvement of HTAs is crucial to ensure that scientific advice takes into account their evidence requirements, to facilitate decision making 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.

The Agency therefore proposes the following categories of action:

‣ Invest in external communication to better explain and promote PRIME;

‣ Evaluate current capacity and identify areas for increased investment;

‣ Shorten the time between scientific advice, clinical trials and MAA submission;

‣ Collaborate with stakeholders to ensure efficient oversight post-approval;

‣ Leverage collaboration with patients, healthcare professionals, academia and international partners.

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 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, 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. 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, these new 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, for example, adequate oversight of the computer software used to control these new processes. The Agency is thus proposing that the system should:

‣ Recruit expertise in novel manufacturing technologies to enhance the assessment process;

‣ Identify bottlenecks and propose modernisation of relevant regulations to facilitate novel manufacturing;

‣ Address regulatory challenges in point-of-care manufacturing, e.g. concept of batch control, role of the Qualified Person;

‣ Facilitate a flexible approach in application of Good Manufacturing Practice.

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

According to the legal definitions of medical devices and pharmaceuticals, products with a medical purpose are either regulated as medicinal products or medical devices depending on whether or not their principal intended mode of action is pharmacological, immunological or metabolic. However, an increasing number of complex products are emerging that combine a medicine and a medical device, and it is becoming ever more difficult to attribute one primary mode of action to these or separate the contribution of biological/pharmacological and physicochemical mechanisms to clinical benefit/risk. In addition, innovative medicines may depend on the use of associated in vitro diagnostics.

Therefore, EMA sees the need for an integrated competence and expertise in such borderline situations to support development of innovative products that will result in significant patient benefit and, at the same time, enhance the growth of a major health sector in Europe. The risk/benefit assessment of such products must evaluate both components, while avoiding unnecessary regulatory burden. This will require collaboration with those notified bodies responsible for regulating medical devices.

To create such an integrated evaluation pathway, the Agency proposes to:

‣ Define how benefit-risk of borderline products is assessed and communicated;

‣ Enrich expertise at the interface between medicines, medical devices and borderline products;

‣ Facilitate the regulatory pathway between notified bodies and medicines' regulators;

‣ 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.

However they also pose a number of challenges, some of which overlap with those of recommendation 3.1.5, above. Such products are particularly likely to be borderline medical devices, in which the contribution of biological/pharmacological and physicochemical mechanisms is hard to distinguish. 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;

▸ Generate guidance addressing PK/PD requirements and long-term efficacy and safety;

▸ Develop guidance on regulatory pathways with device regulators and notified bodies.

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 guidance will bring more tailored treatments for patients faster, thus 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 made consistent throughout the development and decision making phases for a product. This means bearing in mind the different demands of developers, 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 advisory platforms so that product-driven advice can address multiple development options. To this end it proposes to:

▸ Promote more integrated medicines development aligning scientific advice, clinical trials approval and Good Clinical Practice oversight;

▸ Create complementary and flexible advice mechanisms to support innovative product development expanding multi-stakeholder consultation platforms;

▸ 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	‣ Stimulate developers to use novel pre-clinical models, including those adhering to the 3Rs; ‣ Re-focus the role of the 3Rs working group to support method qualification; ‣ Encourage implementation of IT tools to exploit the added value of SEND for the re-analyses of non-clinical studies to support both clinical trials authorisation FIM (first-in-man) and risk minimisation across EU.
Foster innovation in clinical trials	‣ Drive adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance; ‣ Critically assess the clinical value of new and emerging endpoints and their role in facilitating patients' access to new medicines; ‣ Work with stakeholders to encourage collaborative clinical trials; ‣ Collaborate with international partners in ongoing initiatives such as the Clinical Trial Transformation Initiative and ICH.

Develop the regulatory framework for emerging clinical data generation	▸ Develop methodology to incorporate clinical care data sources in regulatory decision-making;
	▸ 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.
Expand benefit-risk assessment and communication	▸ Expand the benefit-risk assessment by incorporating patient preferences;
	▸ Develop the capability to analyse Individual Patient Data to support decision-making;
	▸ Promote systematic application of structured benefit-risk methodology and quality assurance systems across the network;
	▸ Improve communication with HTAs and payers regarding therapeutic context, comparison vs. placebo/active-control, patient perspective;
	▸ Enhance structured benefit/risk assessment to improve communication to the public;
	▸ Incorporate academic research into evidence-based benefit-risk communication.
Invest in special populations initiatives	▸ Focus on speedy access for patient (sub-)populations in urgent need
	» Identify areas of highest unmet needs where clinical care data can supplement clinical trial data
	» Enhance multi-stakeholder advice in collaboration with patients, HCPs, payers and HTAs;
	▸ Progress implementation of the joint EMA/EC paediatric medicines action plan;
	▸ Progress implementation of the geriatric strategic plan;
	▸ Develop a strategic initiative in maternal-fetal health.

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;
	▸ 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.
Exploit digital technology and artificial intelligence in decision making	▸ Establish a dedicated AI test "laboratory" to explore the application of innovative digital technology to support data-driven decisions across key business processes;
	▸ Develop capacity and expertise across the network to engage with digital technology, artificial intelligence, cognitive computing, and their applications in the regulatory system.

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 strategy, intended to replace, reduce and refine animal testing.

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

▸ Stimulate developers to use novel pre-clinical models, including those adhering to the 3Rs;

▸ Re-focus the role of the 3Rs working group to support method qualification;

▸ Encourage implementation of IT tools to exploit the added value of SEND[1] for the re-analyses of non-clinical studies to support both clinical trials authorisation FIM (first-in-man) and risk minimisation across EU.

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. 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' 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.

Novel designs and data sources require adapted statistical methodologies for their planning and analysis. In addition, 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 other bodies involved to ensure that innovative designs meet the needs of all stakeholders.

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

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[1] Standard for Exchange of Nonclinical Data

- Drive adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance;

- Critically assess the clinical value of new and emerging endpoints and their role in facilitating patients' access to new medicines;

- Work with stakeholders to encourage collaborative clinical trials;

- Collaborate with international partners in ongoing initiatives such as the Clinical Trial Transformation Initiative and ICH.

3.2.3 Develop the regulatory framework for emerging clinical data generation

The use of digital technologies in clinical trials has the potential to change not only the way data are produced and collected in clinical trials, but also the nature of the data itself (so-called 'big data', in which the rate and volume of data collected means it is not susceptible to classical methods of analysis). Data from mobile and wearable technology are expected to have a major impact on health in the next five years and such technology offers opportunities such as improved patient access to trials (remote participation), development of novel endpoints, and easier incorporation of patient reported outcomes.

However, there is limited experience of such technology in the medicines regulatory system, and such technologies also carry the risk of collecting data that are not relevant or have to be eliminated as noise. Additionally, there is the overriding need to safeguard patients' data privacy and security. 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;

- 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.

3.2.4 Expand benefit-risk assessment and communication

EMA is recommending work to further improve the way benefit-risk decisions are made and communicated, building on the template improvements already made in its assessments, such as the introduction of a benefit-risk table into public assessment reports. There is much interest from regulators and stakeholders in finding ways to better incorporate patient data (i.e. patient preferences, PRO, etc. – see also recommendation 3.3.3) into benefit-risk evaluation.

However, even where benefit-risk is positive, health economic considerations play a major role in determining subsequent patient access. The challenges for the future include finding ways to express the elements of benefit-risk decisions in a way that assists subsequent stakeholders such as HTAs and payers to make their decisions, thus avoiding widening the gap between regulatory approval and HTA/payers' decisions. Regulators must also continue developing ways to communicate the basis for their decisions to the public, to enable informed decision making and combat misinformation.

The recommended underlying actions are, therefore:

- Expand the benefit-risk assessment by incorporating patient preferences;

- Develop the capability to analyse Individual Patient Data to support decision-making;

- Promote systematic application of structured benefit/risk methodology and quality assurance systems across the network;

- Improve communication with HTAs and payers regarding therapeutic context, comparison vs. placebo/active-control, patient perspective;

- Enhance structured benefit/risk assessment to improve communication to the public;

- Incorporate academic research into evidence-based benefit-risk communication.

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, and childbearing women). Action in geriatric medicine (also currently ongoing) has led to increased awareness of the issue in medicines assessments, and work on additional pharmacovigilance and risk minimisation measures in pregnancy 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 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, new marketing applications still often fail to include sufficient data from elderly patients, and work in understanding the consequences of medicines exposure during pregnancy needs to be intensified and broadened.

The Agency proposes the following actions:

- Focus on speedy access for patient (sub-) populations in urgent need

- Identify areas of highest unmet needs where clinical care data can supplement clinical trial data

- Enhance multi-stakeholder advice in collaboration with patients, HCPs, payers and HTAs;

- Progress implementation of the joint EMA/EC paediatric medicines action plan;

- Progress implementation of the geriatric strategic plan;

- Develop a strategic initiative in maternal-fetal health.

3.2.6 Optimise capabilities in modelling, simulation and extrapolation

Use of modelling, simulation and extrapolation between populations can improve the efficiency of medicines development by reducing the need for, and improving the design of, preclinical and clinical studies. Modelling and simulation (using mathematical, graphical or algorithmic representations of real life systems to study, predict or optimise the behaviour of those systems) are increasingly being used to support the life-cycle management of medicines, while it is foreseen that principles being developed for extrapolation of data from other populations to children may be extended to other areas of medicines development.

For such approaches to enjoy broad uptake, endorsement is needed from other regulators internationally (e.g. via ICH) and from key decision makers such as HTAs and payers. Increased interactions and informed decision-making between scientific disciplines, stakeholders and EMA Committees will be needed.

EMA therefore proposes the following actions:

- Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects;

- 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.

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 a major challenge. Cognitive computing tools that specialise in the processing and analysis of large, unstructured datasets offer a potential solution. EMA is recommending initiatives to exploit digital technology and artificial intelligence and understand how such data and analysis can be used to support regulatory decision-making.

However, even though cognitive computing is rapidly advancing in other industries, it is still in its infancy in the pharmaceutical domain. There is a need to develop cognitive computing tools to accelerate our ability to turn big data into meaningful scientific insight and activity. To ensure such tools are effective and appropriate for use they will need to be developed through close collaboration between disciplinary scientists and computer scientists.

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

- Establish a dedicated AI test "laboratory" to explore the application of innovative digital technology to support data-driven decisions across key business processes;

- Develop capacity and expertise across the network to engage with digital technology, artificial intelligence, cognitive computing, and their applications in the regulatory system.

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, high-quality 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	▸ Ensure the evidence needed by HTAs and payers is incorporated early in drug development plans; ▸ 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; ▸ Contribute to the identification of priorities for HTA; ▸ Monitor the impact of decision-maker engagement through reviews of product-specific experience.

Bridge from evaluation to access through collaboration with payers	▸ Contribute to the preparedness of healthcare systems by creating opportunities for collaboration on horizon scanning;
	▸ Enable involvement of payers' requirements in the prospective discussion of evidence generation plans;
	▸ Clarify the treatment-eligible patient population included in the labelling, and its scientific rationale;
	▸ Participate in discussions clarifying the concept of unmet medical need.
Reinforce patient relevance in evidence generation	▸ Enhance patient involvement in EMA scientific committees;
	▸ Coordinate Agency's approach to patient reported outcomes (PROs). Update relevant clinical guidelines to include reference to PROs addressing study objectives, design and analysis;
	▸ While validating PROs, address patients' needs and leverage patients' expertise;
	▸ Co-develop with HTAs a core health-related quality-of-life PRO to implement in trials and to bridge the gap with comparative effectiveness assessment;
	▸ Explore additional methodologies to gather and use patient data from the wider patient community during benefit-risk evaluation.
Promote use of high-quality real-world data (RWD) in decision making	▸ Create a sustainable, quality assured, flexible framework delivering rapid access to and analysis of representative, longitudinal RWD throughout a product's lifecycle;
	▸ Develop a capacity that will enable the Agency to rapidly and securely access and analyse large amounts of healthcare data;
	▸ Accelerate the implementation of a learning regulatory system based on electronic health records and other routinely collected clinical care data (including RWD).
Develop network competence and specialist collaborations to engage with big data	▸ Implement the core recommendations emerging from the HMA-EMA Joint Big Data Taskforce addressing areas such as harmonisation of data standards, characterisation of data quality, and provision of regulatory guidance as to acceptability of evidence;
	▸ Engage proactively with new stakeholders relevant to the big data landscape;
	▸ Invest in capacity building across the network to acquire new skills to engage with these emerging areas.

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 and patients, develop a strategic plan to deliver the ePI programme;
	▸ Enable the reuse of structured medicinal product information by third parties through development of a standardised interface;
	▸ Address the need for PI content improvements identified in the EC report *(COM(2017) 135 final)*, such as package leaflet layout and readability.
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 external engagement and communications to promote trust and confidence in the EU regulatory system	▸ Develop content strategy, particularly in key public health areas and hot topics in regulatory science
	» Enhance professional outreach through scientific publications & conferences
	» Proactive approach to key public-health areas (e.g. vaccines)
	» Improved communications for patients, healthcare professionals, HTAs and payers;
	▸ Develop more targeted and evidence-based communication facilitated by updated web content and format.

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 the remit and perspectives of all sides.

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. Regulators must also ensure, through engagement with HTAs and other stakeholders, that as new standards and guidelines are developed to meet scientific and technical advances we avoid divergences in evidential standards. Collaboration on priority setting and identifying areas where

engagement is particularly beneficial will help guide appropriate deployment of resources.

The Agency therefore proposes to implement the following actions:

▸ Ensure the evidence needed by HTAs and payers is incorporated early in drug development plans;

▸ 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;

▸ Contribute to the identification of priorities for HTAs;

▸ Monitor the impact of decision-maker engagement through reviews of product-specific experience.

3.3.2 Bridge from evaluation to access through collaboration with payers

As noted in 3.3.1 above, 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.

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 exploration of ways to share horizon scanning activities (key to understanding future resource implications), and discussions on evidence generation with HTAs as well: the ultimate aim of the latter would be to enable one single evidence generation plan to collect the information needed by everybody. Understanding of 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:

▸ Contribute to the preparedness of healthcare systems by creating opportunities for collaboration on horizon scanning;

▸ Enable involvement of payers' requirements in the prospective discussion of evidence generation plans;

▸ Clarify the treatment-eligible patient population included in the labelling, and its scientific rationale;

▸ Participate in discussions clarifying the concept of unmet medical need.

3.3.3 Reinforce patient relevance in evidence generation

Patients bring real-life experience, as well as specific knowledge and expertise, to scientific discussions on medicines and on the impact of regulatory decisions. EMA has incorporated methodologies to capture the patient voice all along the regulatory lifecycle of a medicine, reflecting the priority it places on such engagement.

The Agency is also looking at complementary methods to generate patient data (see section 3.2.4). There are great opportunities arising from new communication tools and the science of patient reporting. EMA is already seeing use of patient-reported outcomes (PROs/PROMs - the reporting of disease state, or treatment, made by the patient) as endpoints within marketing authorisation applications, and given other trends such as eHealth, precision medicine and the drive to outcome-based healthcare, their use will likely continue to grow. Understanding how to use them well will be important.

To reinforce patient relevance in evidence generation, EMA therefore proposes that the following actions should be implemented:

▸ Enhance patient involvement in EMA scientific committees;

- Coordinate the Agency's approach to patient reported outcomes (PROs). Update relevant clinical guidelines to include reference to PROs addressing study objectives, design and analysis;

- While validating PROs, address patients' needs and leverage patients' expertise;

- Co-develop with HTAs a core health-related quality-of-life PRO to implement in trials and to bridge the gap with comparative effectiveness assessment;

- Explore additional methodologies to gather and use patient data from the wider patient community during benefit-risk evaluation.

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 benefit of using RWD to generate complementary evidence across the product life cycle and is committed to promote the use of high quality RWD in decision-making.

However, 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. As noted in some other recommendations, there are additional needs to ensure privacy and security of the data, and governance models must address these.

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

- Create a sustainable, quality assured, flexible framework delivering rapid access to and analysis of representative, longitudinal RWD throughout a product's lifecycle;

- Develop a capacity that will enable the Agency to rapidly and securely access and analyse large amounts of healthcare data;

- Accelerate the implementation of a learning regulatory system based on electronic health records and other routinely collected clinical care data (including RWD).

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 both in health and disease. If analysed appropriately, these new sources of data may 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.

To support the development of the necessary competences, the Agency proposes to do the following:

- Implement the core recommendations emerging from the HMA-EMA Joint Big Data Taskforce addressing areas such as harmonisation of data standards, characterisation of data quality, and provision of regulatory guidance as to acceptability of evidence;

- Engage proactively with new stakeholders relevant to the big data landscape;

- Invest in capacity building across the network to acquire new skills to engage with these emerging areas.

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 and following discussion with representatives of these stakeholder groups and the European Commission, EMA has developed an action plan to improve the EU product information. One key element in this plan is to explore how electronic means can be used to improve access to medicines information by patients and healthcare professionals. This would allow for immediate updating on key safety or efficacy issues, and personalisation of information according to patients' needs, potentially resulting in more informed decisions and better adherence to treatment.

EMA therefore recommends that work to implement real-time electronic product information should be continued and developed, taking into account the key principles to be agreed by EMA, national medicines regulators and EC together with all stakeholders in 2019. 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 and patients, develop a strategic plan to deliver the ePI programme;

- Enable the reuse of structured medicinal product information by third parties through development of a standardised interface;

- Address the need for PI content improvements identified in the EC report (*COM(2017) 135 final*)[2], such as package leaflet layout and readability.

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 serve to 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 high-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.

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[2] https://ec.europa.eu/health/sites/health/files/files/documents/2017_03_report_smpc-pl_en.pdf

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 healthcare professionals and patients, and issuing external communications 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. 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, particularly in key public health areas and hot topics in regulatory science

  » Enhance professional outreach through scientific publications & conferences

  » Proactive approach to key public-health areas (e.g. vaccines)

  » Improved communications for patients, healthcare professionals, HTAs and payers;

- Develop more targeted and evidence-based communication facilitated by updated web content and format.

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

The Agency's regulatory mission is to protect human and animal health. 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 existing 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, licensed for particular conditions, to see if they can be used in other conditions 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	▸ Coordinate scientific and regulatory activities within the EU network; ▸ Evaluate preparedness for emerging pathogens and 'disease X'; ▸ Coordinate discussions with the EU network, international partners and stakeholders on the identification, development, authorisation and post-authorisation follow-up of relevant medicinal products; ▸ Effective and timely communication to healthcare professionals, the public and regulatory partners.

Continue to support development of new antibacterial agents and their alternatives	▸ Evolve regulatory guidance and support alternative approaches to new antibacterial drug development and innovative approaches for prevention and treatment of infections;
	▸ Support initiatives, such as the clinical trials network, to facilitate and accelerate clinical development;
	▸ Encourage new business models that provide "pull" incentives beyond the current "funding research" strategy in the EU;
	▸ In collaboration with HTAs and payers, define the evidence requirements for new antibacterial medicines;
	▸ Support the development and application of rapid diagnostic tools.
Promote global cooperation to anticipate and address supply problems	▸ 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;
	▸ Enhance collaboration with WHO 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 healthcare professionals, patients and consumers organisations and the industry 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.
Support innovative approaches to the development, approval and post-authorisation monitoring of vaccines	▸ Advance methods/tools (e.g. biomarkers) to characterise immune response and to support definition of vaccine quality attributes;
	▸ Examine innovative clinical trial approaches to expedite vaccine development;
	▸ Engage with public health authorities and NITAGs to better inform vaccine decisions;
	▸ 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.

Support the development and implementation of a repurposing framework	▸ Enhance regulatory advice on evidence generation and MAA submission;
	▸ Frame suitability of 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 upport 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.

International cooperation and close liaison and communication with the network and our stakeholders will be key in ensuring preparedness. In terms of preparedness, there is a need to define the scientific evidence to allow regulatory appraisal 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:

▸ Coordinate scientific and regulatory activities within the EU network;

▸ Evaluate preparedness for emerging pathogens and 'disease X';

▸ Coordinate discussions with the EU network, international partners and stakeholders on

the identification, development, authorisation and post-authorisation follow-up of relevant medicinal products;

▸ Effective and timely communication to healthcare professionals, the public and regulatory partners.

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 strategy 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:

▸ Evolve regulatory guidance and support alternative approaches to new antibacterial drug development and innovative approaches for prevention and treatment of infections;

- Support initiatives, such as the clinical trials network, to facilitate and accelerate clinical development;

- Encourage new business models that provide "pull" incentives beyond the current "funding research" strategy in the EU;

- In collaboration with HTAs and payers, define the evidence requirements for new antibacterial medicines;

- Support the development and application of rapid diagnostic tools.

- Promote greater knowledge exchange with international stakeholders on shortages due to quality/manufacturing issues;

- Continue to engage with healthcare professionals, patients and consumers organisations and the industry 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.

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 refers not only to supply chain disruptions (e.g. manufacturing problems) in authorised and 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;

- Enhance collaboration with WHO in the area of supply disruptions due to manufacturing quality issues;

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:

- Advance methods/tools (e.g. biomarkers) to characterise immune response and to support definition of vaccine quality attributes;

- Examine innovative clinical trial approaches to expedite vaccine development;

- Engage with public health authorities and NITAGs[3] to better inform vaccine decisions;

- 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.

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[4], 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 reduce the time and costs of development and offer additional therapeutic options to patients.

Supporting repurposing requires consideration of several areas: the potential incentives and disincentives; the sources of evidence supporting re-purposing; the involvement of academia; potential for imposition of changes to a marketing authorisation and 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 regulatory advice on evidence generation and MAA submission;

- Frame suitability of 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.

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[3] National Immunisation Technical Advisory Groups
[4] Commission Expert Group on Safe and Timely Access to Medicines for Patients

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 academia to undertake fundamental research in strategic areas of regulatory science	▸ Identify, in consultation with academia and relevant stakeholders, fundamental research topics in strategic areas of regulatory science (such as PROs, omics-based diagnostics, drug-device combinations, modelling and simulation, Big Data, and artificial intelligence); ▸ Proactively engage with DG Research & Innovation, DG-SANTE, IMI and Member State funding agencies to propose and issue calls to establish research collaborations.
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 (such as diagnostics, precision medicine, distributed manufacturing, wearable devices, drug re-purposing); ▸ Ensure close interaction between network scientists and academia 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).
Identify and enable access to the best expertise across Europe and internationally	▸ Invest in a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle; ▸ Facilitate more flexible access to global expertise in regulatory science and increasingly specialised and new areas of innovation.

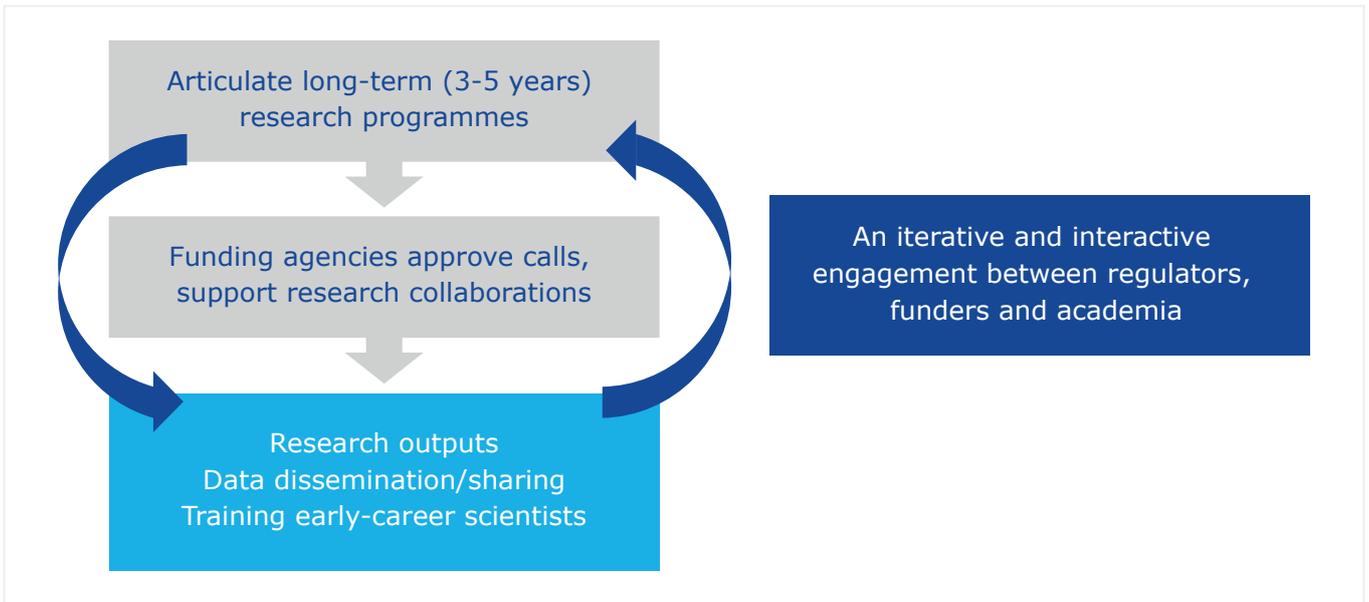| **Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders**	‣ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient;
	‣ Conduct horizon scanning in 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.

Figure 1. Network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science

3.5.1 Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science

Regular, iterative engagement is required between regulators, funders, and academia in order to develop partnerships for undertaking research in selected areas of regulatory science (see Figure 1).

The aim is to provide a mechanism for scientists in the regulatory network and academia to collaborate in identifying and tackling fundamental research questions of high relevance. 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:

‣ Identify, in consultation with academia and relevant stakeholders, fundamental research topics in strategic areas of regulatory science (such as PROs, omics-based diagnostics, drug-device combinations, modelling and simulation, big data, and artificial intelligence);

‣ Proactively engage with DG Research & Innovation, DG-SANTE, IMI and Member State funding agencies to propose and issue calls to establish research collaborations.
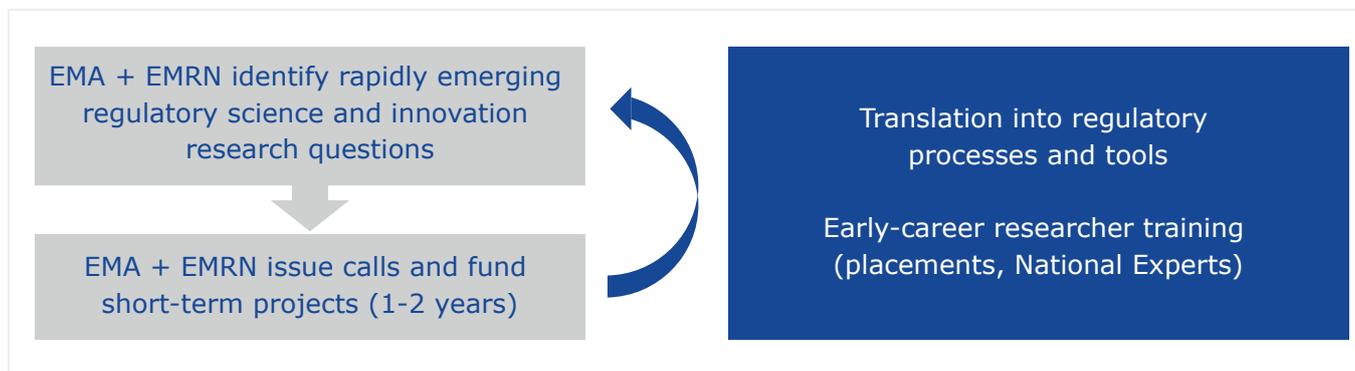
Figure 2. Collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

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

The collaboration in basic science in 3.5.1 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 (see Figure 2).

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 (such as diagnostics, precision medicine, distributed manufacturing, wearable devices, drug re-purposing);

‣ Ensure close interaction between network scientists and academia 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).

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:

‣ Invest in a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle;

‣ Facilitate more flexible access to global expertise in regulatory science and increasingly specialised and new areas of innovation.

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 regulatory science benefits the training needs of the network while academia gains the teaching tools with which to establish new course offerings in medicines development and regulatory science. In addition, as such learning materials and courses are developed, a body of motivated postgraduate students is created, whose work supplies the necessary horizon scanning for innovation in regulatory science and regulatory tools.

To facilitate such dissemination and exchange, EMA proposes to:

▸ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to patient;

▸ 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

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.

Stakeholder input is sought in refining, developing and prioritising these goals, recommendations and actions.

4.1 Goal 1: Catalysing the integration of science and technology in drug 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 drug development	
Core recommendations	*Underlying actions*
Transform the regulatory framework for innovative veterinary medicines	▸ Draft an annex to the new veterinary legislation that defines proportionate and future-proofed technical standards for novel veterinary therapies, particularly biologicals; ▸ Develop standards for novel therapies and the promotion of new endpoints for the evaluation of efficacy; ▸ Strengthen support to industry 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.
Reinforce and further embed application of the 3Rs principles	▸ Apply the highest possible 3Rs standards when implementing the new veterinary regulation; ▸ Strengthen cooperation with European and international institutions; ▸ Motivate increased data-sharing by industry to reduce animal use in safety evaluations; ▸ Encourage medicines' developers to seek qualification of biomarkers that avoid the need for animal studies; ▸ Promote in-silico methodology (e.g. modelling) and novel in vitro assays to reduce animal use, particularly in toxicology/epidemiology and batch control; ▸ Explore whether international recognition of qualification of alternative methods strengthens the use of 3Rs principles.

Facilitate implementation of novel manufacturing models	▸ Recruit expertise in novel manufacturing technologies to enhance the assessment process;
	▸ Identify bottlenecks and propose modernisation of relevant regulations to facilitate novel manufacturing;
	▸ 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;
	▸ Facilitate a flexible approach in application of Good Manufacturing Practice with respect to novel therapies.

4.1.1 Transform the regulatory framework for innovative veterinary medicines

Regulatory science support to novel veterinary therapies is largely demand-led. However, current regulatory paradigms and technical requirements are not well adapted to the challenges presented by new types of 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, meaning that they are almost certain to 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 and reduce duplication and divergence in regulatory approaches and guidance.

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

▸ Draft an annex to the new veterinary legislation that defines proportionate and future-proofed technical standards for novel veterinary therapies, particularly biologicals;

▸ Develop standards for novel therapies and the promotion of new endpoints for the evaluation of efficacy;

▸ Strengthen support to industry 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 do so. The '3Rs' principles envisage 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, such as 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 predictive ability. 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, and EMA is thus proposing the following actions:

‣ Apply the highest possible 3Rs standards when implementing the new veterinary regulation;

‣ Strengthen cooperation with European and international institutions;

‣ Motivate increased data-sharing by industry to reduce animal use in safety evaluations;

‣ Encourage medicines' developers to seek qualification of biomarkers that avoid the need for animal studies;

‣ Promote in-silico methodology (e.g. modelling) and novel in vitro assays to reduce animal use, particularly in toxicology/epidemiology and batch control;

‣ Explore whether international recognition of qualification of alternative methods strengthens the use of 3Rs principles.

4.1.3 Facilitate implementation of novel manufacturing models

Technological development is allowing new and more efficient ways of manufacturing medicines, including 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 enhanced process automation. In turn, smaller manufacturing sites and distributed manufacturing are possible, including use of techniques such as 3D printing that may in the future allow on-site tailoring of manufacturing to individual animals.

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.

The Agency is proposing that the system should:

‣ Recruit expertise in novel manufacturing technologies to enhance the assessment process;

‣ Identify bottlenecks and propose modernisation of relevant regulations to facilitate novel manufacturing;

‣ 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;

‣ Facilitate a flexible approach in application of Good Manufacturing Practice with respect to novel therapies.

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 and improving the scientific quality of evaluations	
Core recommendations	*Underlying actions*
Update Environmental Risk Assessments in line with the latest scientific knowledge	▸ Contribute to the evaluation of novel approaches to ERA and examine the feasibility of establishing active substance monographs;
	▸ Develop further guidance on when the use of persistent, bioaccumulative and toxic substances can be justified;
	▸ Develop additional guidance on the ERA of active substances used in aquaculture, including use of antimicrobials under the 'prescribing cascade';
	▸ Cooperate with DG RTD to fund relevant ERA-related research in veterinary medicines, such as antimicrobial resistance in the environment, and endocrine disruptors;
	▸ Provide scientific support to the European Commission and the EU network to ensure that a "One Health" approach is applied to ERA, and particularly to antimicrobial resistance;
	▸ Increase cooperation in the field of ERA with European agencies, particularly ECHA and EFSA, and establish cooperation with international institutions, academic organisations and initiatives ;
	▸ Strengthen capacity and capability to evaluate the environmental fate and effects of novel veterinary therapies, to consider ERA in the risk/benefit assessment of a product, 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 safety of novel biological substances;
	‣ Monitor evolution of relevant methodologies to evaluate the safety of veterinary medicinal products - including establishment of MRLs where appropriate - to further align the approach of the EU network with other European and international bodies;
	‣ Increase capability in modelling, simulation and extrapolation (with applications in toxicological assessment, dose optimisation, environmental fate and residue depletion);
	‣ Work with DG RTD to fund research relevant to safety evaluation, such as developing robust methods to classify uncertainties;
	‣ Investigate with EU and international partners the combined effects of residues in the food chain;
	‣ Enhance cooperation between European institutions on the safety evaluation of dual-use substances;
	‣ Motivate increased data-sharing by industry to reduce animal use in safety evaluations;
	‣ Improve communication on the safety evaluation of residues to enhance public understanding of EMA's role.
Collaborate with stakeholders to modernise veterinary pharmacoepidemiology and pharmacovigilance	‣ Motivate increased international and stakeholder involvement in pharmacovigilance;
	‣ Using data on the sales of veterinary products made available, develop methodology to collate, analyse and communicate information about the incidence of adverse reactions related to medicines' use;
	‣ Develop methodology to analyse the results of signal detection and improve communication of veterinary pharmacovigilance to the general public;
	‣ 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 mobile phone apps, to increase reporting rates of adverse events.

Develop new and improved communication and engagement channels and methods to reach out to stakeholders	▸ Ensure authoritative communication on key issues, such as unfounded product 'scares';
	▸ Clearly inform the public of the scientific underpinning of new technologies approved, such as biological products including DNA vaccines or gene therapy;
	▸ Promote the presentation of medicinal product information that is readily and easily accessible and able to be updated rapidly, making best use of new and digital technologies;
	▸ Address the problem of under-reporting in pharmacovigilance using new communication approaches.
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, rather than the health of the individual animal;
	▸ Promote systematic application of structured benefit-risk methodology and quality assurance systems across the network;
	▸ Develop criteria to accept non-conventional sources of data;
	▸ Collaborate with regulators of human medicinal products to develop methodology to evaluate the efficacy of a veterinary medicine which is used to produce an improvement in human health;
	▸ Optimise quality and consistency of outputs from EMA and maximise their dissemination to relevant stakeholders.

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

The new veterinary regulation will require an evaluation by the European Commission, supported on request by EMA, of different approaches to strengthen environmental risk assessments (ERAs). This includes the feasibility of establishing a monograph system for all substances, including legacy substances originally marketed before an ERA became mandatory. Although there is some short-term cost from establishing such information on active substances, which may impact on access to medicines, in the longer term both developers and regulators would benefit from the availability

of better data. 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 new veterinary regulation also includes provisions that aim to limit the use of persistent, bioaccumulative and toxic substances in veterinary medicinal products 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. 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[5]' context. EMA therefore proposes these actions:

▸ Contribute to the evaluation of novel approaches to ERA and examine the feasibility of establishing active substance monographs;

▸ Develop further guidance on when the use of persistent, bioaccumulative and toxic substances can be justified;

▸ Develop additional guidance on the ERA of active substances used in aquaculture, including use of antimicrobials under the 'prescribing cascade';

▸ Cooperate with DG RTD to fund relevant ERA-related research in veterinary medicines, such as antimicrobial resistance in the environment, and endocrine disruptors;

▸ Provide scientific support to the European Commission and the EU network to ensure that a "One Health" approach is applied to ERA, and particularly to antimicrobial resistance;

▸ Increase cooperation in the field of ERA with European agencies, particularly ECHA and EFSA, and establish cooperation with international institutions, academic organisations and initiatives[6];

▸ Strengthen capacity and capability to evaluate the environmental fate and effects of novel veterinary therapies, to consider ERA in the risk/ benefit assessment of a product, 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

Pharmaceutically active substances for use in food-producing animals may not be included in authorised veterinary medicinal products unless maximum residue limits (MRLs) have been established following a scientific evaluation by EMA's Committee for Veterinary Medicinal Products (CVMP). MRLs are designed to ensure that consumers are not exposed to harmful levels of pharmacologically active substances[7] via the diet. Some active substances are deemed hazardous at any level and thus prohibited for use in food-producing animals.

In the coming years, it is anticipated that the MRL framework will need to be adapted for novel biologicals, and to better assess the consumer safety risks associated with endocrine-disrupting chemicals. The cumulative risk of exposure to residues from multiple active substances and sources will also need study, as current approaches for setting MRLs only focus on exposure to individual chemicals. Additional development is likely to be driven by pressure to align MRL methodology across different regulatory and regional frameworks, where methodologies employed are, in some cases, considerably more complicated and resource-demanding than those employed by CVMP. The Agency therefore proposes the following actions:

▸ Develop methodology to evaluate the safety of novel biological substances;

▸ Monitor evolution of relevant methodologies to evaluate the safety of veterinary medicinal products - including establishment of MRLs where appropriate - to further align the approach of the EU network with other European and international bodies;

▸ Increase capability in modelling, simulation and extrapolation (with applications in toxicological assessment, dose optimisation, environmental fate and residue depletion);

▸ Work with DG RTD to fund research relevant to safety evaluation, such as developing robust methods to classify uncertainties;

▸ Investigate with EU and international partners the combined effects of residues in the food chain;

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[5] http://www.who.int/features/qa/one-health/en/

[6] For example, OECD, WHO, the UN Food and Agriculture Organization, and the Society of Environmental Toxicology and Chemistry

[7] https://ec.europa.eu/health/veterinary-use/maximum-residue-limits_en

- Enhance cooperation between European institutions on the safety evaluation of dual-use substances;

- Motivate increased data-sharing by industry to reduce animal use in safety evaluations;

- Improve communication on the safety evaluation of residues to enhance public understanding of EMA's role.

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 new veterinary regulation 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:

- Motivate increased international and stakeholder involvement in pharmacovigilance;

- Using data on the sales of veterinary products made available, develop methodology to collate, analyse and communicate information about the incidence of adverse reactions related to medicines' use;

- Develop methodology to analyse the results of signal detection and improve communication of veterinary pharmacovigilance to the general public;

- 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 mobile phone apps, to increase reporting rates of adverse events.

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 and to give veterinary medicines more visibility. Such actions must 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 reader, be it veterinarians or SMEs, 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 creatively to address under-reporting. The EU network must therefore continue to share best practice and ensure consistency. In addition there is a need to improve how the product information for veterinary medicines is conveyed to users. The new veterinary legislation provides for a product package leaflet to be available electronically. This aligns with a key element in the EC report to improve the product information for human medicines, i.e., to explore, in close liaison with stakeholders, how electronic means can be used to improve access. While veterinary medicines are outside the scope of the EC report, progress on ePI for human medicines will also be useful for any future activity for the product information of veterinary medicines. As a result, the EU network will look at the impact of the new veterinary legislation on the provision of product information for veterinary medicines. The Agency therefore proposes to:

‣ Ensure authoritative communication on key issues, such as unfounded product 'scares';

‣ Clearly inform the public of the scientific underpinning of new technologies approved, such as biological products including DNA vaccines or gene therapy;

‣ Promote the presentation of medicinal product information that is readily and easily accessible and able to be updated rapidly, making best use of new and digital technologies;

‣ Address the problem of under-reporting in pharmacovigilance using new communication approaches.

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

Although the European assessment of marketing authorisation applications is conducted rigorously, there is a continual need to adapt to innovation in the development of medicinal products and techniques such as ever more sensitive 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 regulation is provided without creating unnecessary barriers.

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 the advantages are often 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 cases.

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, rather than the health of the individual animal;

‣ Promote systematic application of structured benefit-risk methodology and quality assurance systems across the network;

‣ Develop criteria to accept non-conventional sources of data;

‣ Collaborate with regulators of human medicinal products to develop methodology to evaluate the efficacy of a veterinary medicine which is used to produce an improvement in human health;

‣ Optimise quality and consistency of outputs from EMA and maximise their dissemination to relevant stakeholders.

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	▸ Support prudent and responsible use of antimicrobials, via updated and/or new regulatory guidance and scientific opinion;
	▸ Promote authorisation of alternative approaches to the use of conventional antimicrobials;
	▸ Develop novel regulatory paradigms for efficacy, such as measuring a medicinal product's effect at the level of herd rather than in the individual animal;
	▸ Develop a regulatory approach for bactericidal compounds that are not themselves traditional antibiotics;
	▸ Facilitate cooperation between stakeholders in AMR and veterinary vaccine availability;
	▸ Identify funding to generate data, e.g. via modelling and extrapolation, to support existing, including off-patent, antimicrobials;
	▸ Foster development of pen-side and accompanying diagnostics for antimicrobial sensitivity testing;
	▸ Explore linkage of authorisation and use of high-risk antimicrobials with the approval and use of a companion diagnostic.

Coordinate Network activities to improve data collection on antimicrobial use in animals	▶ Define requirements for harmonised data collection on antimicrobial use in animals by species;
	▶ Align standards and methods of data collection to complement those developed internationally;
	▶ Refine the methodology for 'stratification' of sales data to derive and validate estimates of antimicrobial sales by species;
	▶ Develop methodology to collate, analyse and communicate data on antimicrobial use;
	▶ Formulate 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.
Engage with stakeholders to minimise the risks of antiparasitic resistance	▶ Catalyse international cooperation to combat antiparasitic resistance and establish best practice;
	▶ Cooperate with DG RTD to fund research into antiparasitic resistance and its control/prevention;
	▶ Align with EFSA to survey and monitor antiparasitic use in food-producing species;
	▶ Promote responsible use of antiparasitics in the EU and monitor for development of antiparasitic resistance.
Promote and support development of veterinary vaccines	▶ Acknowledge that different benefit-risk approaches are required for assessment of specific vaccine types, especially zoonotic vaccines, minor-use-minor-species vaccines, and vaccines for exceptional circumstances;
	▶ Develop criteria for epidemiological modelling to demonstrate vaccine efficacy against epizootic disease;
	▶ Interact collaboratively with industry to focus development on areas where vaccines are most needed;
	▶ Clarify the criteria required for field efficacy trials to support marketing authorisation applications for new vaccines.

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 Agency 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 patterns of use still vary 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 entails the creation of a 'tool box' 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 man. The Agency anticipates providing input in this area, to supplement ongoing work including the CVMP strategy on antibiotics 2016-2020[8] and its monitoring of the effects of AMR on the benefit-risk assessment of medicines. It will also continue to develop EU and international cooperation on AMR.

Measures will be needed for maintaining availability of existing antimicrobials, repurposing agents new to veterinary use where this does not increase the risk of AMR in humans, and promoting the development of alternative types of treatment such as vaccines. The former 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. Also important will be measures to foster development of rapid, point-of-care, companion diagnostics to allow more rational and targeted choice of therapy. The Agency therefore proposes to:

‣ Support prudent and responsible use of antimicrobials, via updated and/or new regulatory guidance and scientific opinion;

‣ Promote authorisation of alternative approaches to the use of conventional antimicrobials;

‣ Develop novel regulatory paradigms for efficacy, such as measuring a medicinal product's effect at the level of herd rather than in the individual animal;

‣ Develop a regulatory approach for bactericidal compounds that are not themselves traditional antibiotics;

‣ Facilitate cooperation between stakeholders in AMR and veterinary vaccine availability;

‣ Identify funding to generate data, e.g. via modelling and extrapolation, to support existing, including off-patent, antimicrobials;

‣ Foster development of pen-side and accompanying diagnostics for antimicrobial sensitivity testing;

‣ Explore linkage of authorisation and use of high-risk antimicrobials with the approval and use of a companion diagnostic.

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

The EMA is working with the network to collect data to better inform future actions and to achieve the responsible and reduced use of antimicrobials in animals. Inter-Agency reports analysing antimicrobial consumption and resistance analysis are also being produced with increasing frequency.

The new veterinary legislation will require harmonised standards for the submission of data, the quality of which will be much higher than that currently collected. These standards will need to be defined, and must take account of those developed

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[8] https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/cvmp-strategy-antimicrobials-2016-2020

internationally. In addition, the development of improved methodologies to analyse exposure and use of antimicrobials by species is required. EMA therefore proposes to:

▸ Define requirements for harmonised data collection on antimicrobial use in animals by species;

▸ Align standards and methods of data collection to complement those developed internationally;

▸ Refine the methodology for 'stratification' of sales data to derive and validate estimates of antimicrobial sales by species;

▸ Develop methodology to collate, analyse and communicate data on antimicrobial use;

▸ Formulate 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 livestock and companion animals; a significant number of these parasites also have zoonotic potential, and some pose a major health concern in humans (e.g., echinococcosis). In addition, as a consequence of global warming and an increase in the movement of animals, new parasite species are spreading into the EU. This comes along with changes in animal husbandry which have resulted in increased use of antiparasitic substances in livestock (e.g., the change from caged to free-range hens). With this 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 (e.g., antiparasitic treatments for sea lice in farmed salmon).

Various approaches have been suggested to delay resistance development including research to develop new active substances or new fixed combinations of active substances with overlapping activities targeting the same parasites, and changes in drug administration or animal husbandry. However, unlike the situation for antimicrobials, there remain significant knowledge gaps in the understanding of resistance development and an absence of (routine) EU-wide data monitoring systems. There is thus a need for international cooperation to fill these gaps. The Agency therefore proposes to:

▸ Catalyse international cooperation to combat antiparasitic resistance and establish best practice;

▸ Cooperate with DG RTD to fund research into antiparasitic resistance and its control/prevention;

▸ Align with EFSA to survey and monitor antiparasitic use in food-producing species;

▸ Promote responsible use of antiparasitics in the EU and monitor for development of antiparasitic resistance.

4.3.4 Promote and support development of veterinary vaccines

Veterinary vaccines and other 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 antibiotics.

Veterinary vaccines are particularly important to human health as they can prevent zoonoses, and the joint EMA/HMA Task force on availability also includes in its scope veterinary medicines. However, they come with specific challenges in terms of authorization[9] and the following actions are proposed:

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[9] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2015/03/event_detail_001140.jsp&mid=WC0b01ac058004d5c3

- ▸ Acknowledge that different benefit- risk approaches are required for assessment of specific vaccine types, especially zoonotic vaccines, minor-use-minor-species vaccines, and vaccines for exceptional circumstances;

- ▸ Develop criteria for epidemiological modelling to demonstrate vaccine efficacy against epizootic disease;

- ▸ Interact collaboratively with industry to focus development on areas where vaccines are most needed;

- ▸ Clarify the criteria required for field efficacy trials to support marketing authorisation applications for new vaccines.

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 academia to undertake fundamental research in strategic areas of regulatory science	▸ Identify, in consultation with academia and relevant stakeholders, fundamental research topics in strategic areas of regulatory science. For example, 'omics-based diagnostics, drug-device combinations, modelling and simulation, big data, and artificial intelligence; ▸ Proactively engage with DG Research & Innovation, DG-SANTE, DG-AGRI and Member State funding agencies to propose and issue calls to establish research collaborations.
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. For example, diagnostics, alternatives to antimicrobials, emerging zoonotic diseases; ▸ Ensure close interaction between network scientists and academia 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).
Identify and enable access to the best expertise across Europe and internationally	▸ Invest in a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle; ▸ Facilitate more flexible access to global expertise in regulatory science and increasingly specialised areas of innovation.

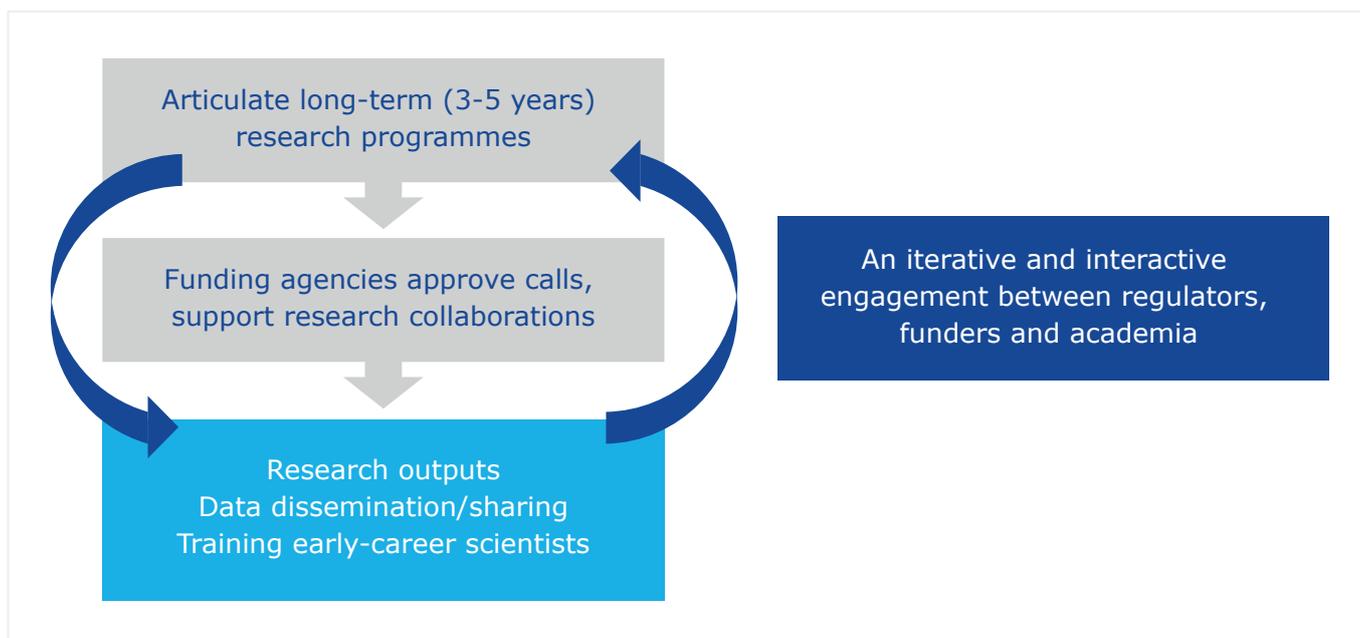| **Disseminate and exchange knowledge, expertise and innovation across the network and to its stakeholders** | ▸ Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to use in animals; |
| | ▸ Conduct horizon scanning in key areas of innovation via collaborations with academia and the EU-Innovation Network; |
| | ▸ Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders. |

Figure 3. Network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science

4.4.1 Develop network-led partnerships with academia to undertake fundamental research in strategic areas of regulatory science

Regular, iterative engagement is required between regulators, funders, and academia in order to develop partnerships for undertaking research in selected areas of regulatory science (see Figure 3).

The aim is to provide a mechanism for scientists in the regulatory network and academia to collaborate in identifying and tackling fundamental research questions of high relevance. 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:

▸ Identify, in consultation with academia and relevant stakeholders, fundamental research topics in strategic areas of regulatory science. For example, 'omics-based diagnostics, drug-device combinations, modelling and simulation, big data, and artificial intelligence;

▸ Proactively engage with DG Research & Innovation, DG-SANTE, DG-AGRI and Member State funding agencies to propose and issue calls to establish research collaborations.

Figure 4. Collaborations between academia and network scientists to address rapidly emerging regulatory science research questions

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

The collaboration in basic science in 4.4.1 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 (see Figure 4).

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. For example, diagnostics, alternatives to antimicrobials, emerging zoonotic diseases;

‣ Ensure close interaction between network scientists and academia 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).

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 new to regulators. 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 becoming ever more specialised.

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

‣ Invest in a knowledge management system to track innovation, share information, enable linkages and create new insights across the product lifecycle;

- Facilitate more flexible access to global expertise in regulatory science and increasingly specialised areas of innovation.

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 regulatory science benefits the training needs of the network while academia gains the teaching tools with which to establish new course offerings in medicines development and regulatory science. In addition, as such learning materials and courses are developed, a body of motivated postgraduate students is created, whose work supplies the necessary horizon scanning for innovation in regulatory science and regulatory tools.

To facilitate such dissemination and exchange, EMA proposes to:

- Engage with academia to develop regulatory training modules, including describing innovation of new medicines and their progression from laboratory to use in animals;

- Conduct horizon scanning in key areas of innovation via collaborations with academia and the EU-Innovation Network;

- Drive a data-sharing culture to foster open science which is mutually beneficial for all stakeholders.

5. Working together: international regulatory science cooperation

Cooperation with regulators outside the EU network is key to much of the vision outlined in the reflection. 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 cooperation. Although multilateral cooperation does require resources, it is ultimately an investment in more efficient resource use, for EMA and its partners.

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 FDA, 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 or AMR. It also aims to ensure harmonised communication on key issues such as unfounded scares.

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 reflection 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

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

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IMI	Innovative Medicines Initiative
MAA	Marketing Authorisation Application
MRL	Maximum Residue Limit
NITAG	National Immunisation Technical Advisory Group
NVR	New Veterinary Regulation
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
PI	Product Information
PK/PD	Pharmacokinetics/Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PRIME	Priority Medicines Scheme
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
RWD	Real World Data
SciCoBo	Scientific Coordination Board
SEND	Standard for Exchange of Nonclinical Data
SME	Small or Medium-sized Enterprise
STAMP	Commission Group on Safe and Timely Access to Medicines for Patients
VICH	Veterinary International Conference on Harmonization
WHO	World Health Organization

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