EMA Regulatory Science Strategy to 2025
Post-consultation Stakeholders Workshop
Human Workshop - **Draft** briefing materials

18 – 19 November 2019
European Medicines Agency
Amsterdam, The Netherlands

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Objectives of the meeting

Further to last year's workshop and a very successful public consultation, we are pleased to inform you of the upcoming multi-stakeholders workshop entitled "EMA Regulatory Science to 2025" which will take place on 18th and 19th November 2019.

The objectives of this workshop are to:

- share the outcome and key messages from the analysis of the public consultation;
- reflect on the likely prioritisation of core recommendations EMA's Regulatory Science Strategy to 2025; and
- identify concrete actions in order to implement the key core recommendations.

Please note that only a sub-set of core recommendations and actions across the strategic goals have been selected to be discussed within the workshop format. These have been selected primarily based on stakeholders' priority ranking of the core recommendations as well as the degree of comments/suggestions received on the underlying actions and proposals for further actions. However, very constructive feedback has also been received on the remaining core recommendations and underlying actions. These will be addressed post workshop such that the final RSS strategy document will present a holistic outcome of the public consultation as well as revised/extended action listings for all core recommendations.

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.

Underlying actions

1.1. Enhance early engagement with novel biomarker developers to facilitate regulatory qualification

- Advice on use of biomarker panels, in addition to advice on individual biomarkers would be beneficial as currently guidance is only on single biomarkers
- Regulatory guidance on the potential utility of new biomarkers under development for use in HD clinical programs, as well as legacy biomarkers, is needed to inform further biomarker development and translate treatments from animal models and pre-clinical studies to clinical trials.
- There is an opportunity to substantially evolve the EMA's biomarker validation process in order to encourage greater uptake and use.
- The existing approach to qualification presents such high barriers to achieving success in a timely manner that it impedes the ability to rapidly develop innovative treatment.
- Develop guidance ensuring a harmonised approach and covering the following fields:
  - Required performance evaluation for different patient risk categories e.g. observational screening vs. patient selection
  - Requirements for concordance/sensitivity testing and bridging studies to "in-house" tests and 2nd generation CDx for CE Marking
  - Requirements for Complementary Diagnostics.
- Guidance is missing on the use of NGS in an investigational setting.
- For novel biomarkers, consideration should be given to enhance the current EMA qualification procedure to allow the procedure to be accelerated and provide for greater flexibility, or a different pathway to develop and discuss biomarker development outside of the qualification procedure to facilitate rapid progress.

1.2. Address the impact of emerging 'omics' methods and their application across the development life cycle

- This goal will require a proactive role from the regulatory bodies supporting public policies addressed at:
  - (i) developing research projects to ensure the quality, completeness, validity and analysis of datasets,
  - (ii) developing informatics, ICT and mathematics tools to integrate, analyse and extract value from databases (e.g. omics, health records, clinical data, imaging data, data from mobile devices and wearable sensors, behavioural, environmental) with specific attention on interoperability of the respective databases. This should include research to ensure the quality, completeness and validity of data.
- Using the concrete example of comprehensive genomic profiling for diagnostic purposes
  - Products in the precision medicine category involve novel complex techniques for which a standard uniform approach to setting performance goals is not appropriate. Indeed, Next Generation Sequencing (NSG) can be used for very different clinical purposes (e.g. differences in disease biology). For example: Germline cells with uniform genetic makeup require a different approach than somatic aberrations with genetic heterogeneity. Therefore, performance metrics should not be uniformly applied, instead they should be fit for purpose.
  - Developing products in the precision medicine category requires a higher level of flexibility compared to more conventional products. Indeed, NGS technology rapidly evolves with continual improvements in accuracy and sensitivity and the introduction of new variants. Therefore, develop a process that allows certain changes to NGS workflow components or claims to be incorporated quickly e.g. by using pre-specified plans and criteria. Future addition of new variants should not require revalidation of validated platform components and should be built on variant identification in well-characterised samples.
  - Support is needed to ensure transparent performance comparability of different assays. This support is needed most in two distinct areas. Firstly, there is a need for global standard reference materials, including input on the characteristics, application, and availability of such material. There should be alignment on the use of reference materials in validating across NGS systems. Secondly, general advice and advice on principles in scientific and regulatory decision-making are needed. Therefore,
  - Transparency - make clear how biomarker and assay performance information are to be provided in the SmPC and companion diagnostics (CDx) label.

1.3. Evaluate, in collaboration with HTAs, payers and patients, the impact of treatment on clinical outcomes measured by biomarkers.

- There is an opportunity to substantially evolve the EMA's biomarker validation process in order to encourage greater uptake and use. Further, the value of new markers is not always evaluated in the same way by HTA bodies, leading to delay in patient access to innovative personalised medicines.

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:

Underlying actions

1.1. Identify therapies that address unmet medical need.

- It is important that the EMA stays current and issues and updates guidelines which should address principles and not be overly prescriptive
- EMA should also consider developing a regulatory framework that will support a multisource environment of ATMPs that will lead to a competitive market and affordable therapies in the future.
- Main obstacles are the disconnection from EU (e.g. centralised procedure) to national legislative framework (e.g. GMO assessment). A more integrated system with cross-fertilisation between science/clinical advances to regulatory and access is essential to support an efficient translation of these innovative products into patient treatments.
- ATMPs emphasize the lack of a holistic and integrative legislative framework, arising from discrepant interpretation with different requirements. Improved coordination between EU legislative authorities responsible of the legislative frameworks applicable to ATMPs would help.
- Rather than looking to identify therapies, the action should be better cooperation with stakeholders (European Commission, national agencies/GMO authorities in the Member States) to ensure that the EU is competitive in the ATMP field so these products can be developed in the EU and there is capacity across the European regulatory network to deal with these products.
- The European Commission is actively addressing the issue of extension of GMO authorization harmonization across the EU community to additional ATMPs (besides human cells genetically modified by means of retro/lentiviral vectors). This is currently discussed within the GMO Interplay WG, where both representatives from NCAs and relevant Ministries are present, and should be included among the actions.

- To leverage existing or provide a new platform for building further continuity between national and EU-level aspects of ATMP development and facilitating increased alignment/convergence between Member States.
- Multi-level regulations: there are still significant inconsistencies between national and European requirements
- Calls for a comprehensive strategy, with a structured and coordinated approach at European and national levels to ensure that Europe can sustain a global leadership role in the research, development, and commercialisation of Advanced Therapies Medicinal Products (ATMPs)

1.2. Provide assistance with early planning, method development and clinical evaluation.

- These should imply a capillary and proactive communication to developers about the usefulness to engage a very early dialogue with the Agency, starting from the classification of their product. This would help in particular small entities to exploit all available tools to rightly orientate their development plan (e.g. CAT ATMP classification, PRIME scheme, SME office, ITF, EU-IN through national Innovation Offices) and would decrease the de-regulated/underground use of these products.
- The rapid pace of the scientific knowledge and process of innovation would merit an efficient continuum of dialogue with stakeholders to allow a more effective way to develop products.
- For example, a dedicated network for ATMPs across regulatory bodies including medicines, medical devices, tissues and cells and environment competent authorities (GMO Bodies).
- EMA can play an important role in fostering increased convergence between Member States and internationally, such as, for instance, ensuring a closer collaboration on these topics with the Heads of Medicines Agencies (HMA) and the EU-Innovation Network (EU-IN).

1.3. Support evidence generation, pertinent to downstream decision-makers.

- EMA should promote further multi-stakeholder discussions to examine how these products are assessed for efficacy/effectiveness compared to symptomatic treatments
- Discussion should cover post-marketing activities as there will be ongoing data generation and the endpoints in a post-approval setting may be different to those in clinical trials supporting a regulatory approval
- These actions should imply early and constant involvement of stakeholders, in particular HTA bodies.

1.4. Address the challenges of decentralised ATMP manufacturing and delivery locations

- Address the challenges of ATMP manufacturing (decentralised manufacturing and delivery locations, expedited quality aspect development, conduction and evaluation of comparability exercise, e.g., manufacturing process changes, new manufacturing site(s) implementation, etc)
- Plasma protein therapies' manufacturing, along with other biologics, could also potentially be decentralized. Does the EMA have plans to address the concept of decentralized manufacturing more broadly beyond ATMPs?

- On various occasions we have noticed that clinical and manufacturing requirements are not easily anticipated by developers. In particular, greater clarity on CMC expectations for submission versus post-marketing commitments would help innovators pursuing expedited pathways for innovative therapies.
- Framework supporting manufacturing innovation: The regulatory framework should be flexible enough to allow adoption of more advanced technology once available and thus continual improvement in the manufacturing processes.

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

- EMA should also consider an investment into the further familiarisation of healthcare professionals with ATMPs.
- Support for cross-sectoral research
- Facilitate 'wet lab' research
- Provide education and training for early stage researchers to increase awareness of regulatory challenges to development and translation
- In general, we would like to ask EMA when evaluating new technologies (especially ATMPs) also take into account the impact on health care setting / patient treatment process as a whole. In situation where technologies would only be available in certain centres in Europe and fragile patients (and their families) would need to travel far from home and stay in foreign hospitals for months might have important impact for the patient outcomes (including quality of life). We believe this is a promising avenue of future work for the Agency.

1.6. NEW! International cooperation

- To engage with other international regulatory agencies to foster global convergence of requirements for ATMP (including their starting/raw materials, methods and classification) and/or to define new common approaches to assess and approve them.
- Leveraging the best international expertise to achieve such convergence is important to achieve common, science-based evaluation methods and criteria.
- Global convergence: EMA is strongly encouraged to engage with other international regulatory agencies to foster global convergence of requirements for ATMP.

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

An increasing number of complex products are emerging that combine a medicine and a medical device, 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.

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.

Underlying actions

1.1. Regulatory requirements and guidance development

1.1.1. Define how benefit-risk of borderline products is assessed and communicated

1.1.2. Facilitate the regulatory pathway between notified bodies and medicines' regulators

1.1.3. International harmonisation

- A clear outline of the roles and responsibilities of Notified Bodies and National Competent Authorities/EMA is essential Therefore, the process for interaction between EMA/National Competent Authorities and NBs as well as the timing of the various assessments should be defined in a procedural guideline which should cover the following points:
  - A mechanism for integrated MAA/NB review process of a drug combined with medical device, or an in vitro diagnostic and managed through a new EMA procedure;
  - Clarification of how information and assessment of the CDx will be shared with EMA/NCAs during the drug approval process, including considerations when assessments are done in parallel;
  - Considerations regarding information from the device, or in vitro diagnostic to be included in the Risk Management Plan, which should be discussed with the PRAC rapporteur;
- Considerations for conditional/accelerated approval scenarios, timing of CDx marketing application;
- Possibility of approval of a therapeutic product without an approved CE marked CDx
- Definition of a mechanism for resolution of conflict in case of misalignments between NBs and EMA/NCA;

- The new database for devices (EUDAMED) should be linked with pharmaceutical databases. Possible consequences for both diagnostic and medicine manufacturers need to be addressed;
- Support is needed to ensure transparent performance comparability of different assays. In particular general advice and advice on principles in scientific and regulatory decision making are needed. Therefore, develop guidance ensuring a harmonised approach and covering the following fields:
  - Requirements for concordance/sensitivity testing and bridging studies to "in-house" tests and 2nd generation CDx for CE Marking
  - Transparency is needed in CDx labeling. should make clear how biomarker and assay performance information are to be provided in the SmPC and CDx label.
- Guidance is missing on the use of companion diagnostics in an investigational setting CTFG. Disparate views of National Competent Authorities may hinder and delay clinical development. Therefore, regulatory guidance + SHs is needed on the appropriate validation requirements.
- The definition by the EMA Inspection group, of an inspection guidance for drug -device combination product/ device constituent and the support for a mutual recognition of inspection with FDA;
- Alignment and harmonisation with other jurisdictions (e.g. FDA) is essential as development of medicinal products and NGS based products is a global enterprise. Primarily device if IVD – joint effort.

1.2. Building network of expertise to provide support throughout the continuum of product development and lifecycle

1.2.1. Enrich expertise at the interface between medicines, medical devices and borderline products

- Particularly important in the context of digital health needs a strong collaboration with the medical device community and Notified Bodies to ensure aspects such as qualification of new digital methodologies for drug development are carried out with the best available expertise and in a holistic manner
- More workshops bringing together industry, regulators and notified bodies, could be extremely helpful, as would on-going training of assessors via case-studies through the EMA network. The continued work of the HMA/CAMD Strategic and Operational groups on this topic would also be appreciated.
- Consider set up of a combination product/device or drug/CDx expert assessment function such as the FDA Office of Combination Products

1.3. Gain insight in innovation on drug-device combination products via horizon scanning

1.4. A mechanism for early interaction with EMA and NBs to obtain joint advice during development and at pre-submission stage;

- It is essential for the developer to have the possibility to gain acceptance of their development plan before it is implemented. It should therefore be possible to ask for development advice from the stakeholders involved in the assessment of these products. By design, this platform should allow

for timely joint advice, involving notified bodies, NCAs and/or EMA, depending on the type of questions.

- A mechanism for timely involvement of Health Technology Assessment bodies in the co-development between medicinal product/in-vitro diagnostic;
- EMA should explore and identify best practices and correlating standards in the areas of product quality and design, clinical validation, patient utilization, and regulatory approval oversight of these novel therapeutics.
- Guidance addressing roles and responsibilities, process, bridging studies and follow on test panels will be key

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:

Underlying actions

1.1. Create complementary and flexible advice mechanisms to support innovative product development also expanding multi-stakeholder consultation platforms

- Rare diseases where companies currently face the challenge to interact with various EMA committees (PDCO, CHMP, SAWP, CAT) at the same time and alignment needs to be found if there is one lean confirmatory study planned.
- Consider how the innovative approach to regulatory dialogue encouraged by the PRIME scheme can be extended.
- Taking the learnings from PRIME, national agency experts could provide advice and lead on to be Rapporteurs allowing integration of the advice from clinical trial through approval and throughout the lifecycle. To enable agility, EU experts would need to be in a position to provide EU scientific advice rather than requiring a formal EU CHMP/SAWP advice procedure. Expanding PRIME eligibility based on non-clinical and tolerability data to non-SME/academia would also be helpful.
- Redesign of a more flexible and integrated R&D product support mechanism, providing agile dynamic advice across the lifecycle of the medicine. Research and development timelines are becoming increasingly efficient and should be matched by the timelier provision of advice. For example, waiting around 4-6 months from the scientific advice request to the meeting with SAWP to occur is not compatible with an expeditious clinical development programme. We would welcome a quicker, voluntary, and flexible engagement with regulators and other stakeholders. The developer should have the ability to select from multiple levels of advice engagement based on the attributes of a particular product.
- Redesign of a more flexible and integrated R&D product support mechanism
- Changing pace and process of innovation along the development continuum. This envisaged dynamic advice is also needed to adaptably accommodate specialised input for specific types of

products (e.g. paediatrics, drug-device combination products). The existing scientific advice process should be improved by promoting a more interactive approach during the procedure and allowing greater access to specialised working groups when novel approaches are proposed. Moreover, this broadening and integration of regulatory advice should progress beyond EMA programmes (e.g., PRIME) to better bridge the advice and decision-making gap across the EU regulatory system (i.e., EMA, EMA's Committees, National Competent Authorities) and beyond (e.g., US FDA).

- The overall value of pan-EU scientific advice is undermined when contradictory opinions emerge during the development of a product. This can be through the different EMA Committees, but also, through the Member-State-led approach to decision-making for clinical trials. This national approach to clinical trials and the EU centralised approach to the provision of scientific advice also mean that there is no unified "line of sight" on the progress of a product during its development from early clinical trials through to approval. This contrasts unfavourably with the U.S. IND system where the FDA provides comprehensive guidance to companies. Consequently, today, companies must attempt to weave together advice given at multiple points along the drug development path. The entire regulatory advice process could gain from greater flexibility, iterative pathways for seeking advice, and integration in a more holistic manner. Early appointment of a Rapporteur, as in PRIME, may be an ideal method to help facilitate flexible, but integrated regulatory advice....
- Format: In addition to the existing process, it should be possible to seek timelier advice on more straightforward questions. For instance, a process similar to Japan PMDA's "Pre-meetings" should be considered. This advice mechanism could allow for a swift turnaround with limited administrative onus, and thereby, allow the medicine's development to progress following the deliberation on basic regulatory questions.
- Provide preliminary feedback ahead of discussion meeting so that the sponsor can also suggest additional topics for discussion based on this feedback. In this way, the developer's discussion topics can be added to those determined by the SAWP/HTA bodies (i.e., a more interactive engagement process between the sponsor and the SAWP).
- Timeliness: Currently, the time required to gain advice can be quite long in the EU. Therefore, a more iterative, flexible approach could allow the timeline for receiving advice to be significantly reduced in these instances. This option should offer even shorter timelines for follow-up questions (e.g., considering new information or changes to the development programme since the initial advice was given).
- Tailored stakeholder input for medicine-device combinations: It should be possible to seek timely joint advice on medicine-medical device combination products by involving notified bodies, NCAs and/or EMA, depending on the questions. The advice opportunities should also be available for medicine and connected device combinations (although some of these products might not currently require an integrated evaluation pathway, they should be considered holistically whilst designing the development approach). Involving these additional stakeholders would also support the EMA proposal to "Create an integrated evaluation pathway for the assessment of medical devices, in vitro diagnostics and borderline products (Rec. 1.5)". Indeed, it is essential for the developer to gain timely, iterative, integrated input into their medicine-device development plan before implementation.
- Ensure wider stakeholder involvement in specific aspects of advice (e.g., CTFG for clinical trials, Notified Bodies for device/drug products)

- Furthermore, a platform to get multi-stakeholder feedback on the digital endpoint should be developed. Current options are the qualification opinion or scientific advice. However, both are lengthy processes that are not adapted to the agility sponsor's need.
- Today PIPs have to be agreed very early on in the development process. This makes the PIP to a great extent rely on assumptions which later, often enough, turn out to have not been very accurate… The timing of PIPs could be more flexible and agreed on during early scientific advice such that they become based more on evidence than as currently on speculative assumptions.
- For prophylactic vaccines, involvement of recommending bodies (NITAGs) is key and not yet routinely possible (only one pilot so far). Insist on the need to consider vaccine specificities when creating multi-stakeholder consultation platforms.
- The details of the pathway should be drafted in collaboration with relevant stakeholders (e.g. through a multi-stakeholder workshop) and tested via a voluntary pilot process.

1.2. Facilitate a more iterative engagement framework that allows for better reflection of the continuum of evidence generation and development decision including making new trends and considerations publicly available.

- Access to early consultation and feedback from regulators prior to submission is extremely valuable in order to build quality dossiers and to anticipate challenges. An ability to have more regular dialogue beyond the relatively bundled and infrequent interactions of periodic scientific advice applications would strengthen the ability of applicants to make quality development choices as needed and to avoid committing to choices which ultimately lead to inefficient regulatory outcomes.
- In complement of more flexible advice mechanisms along the development continuum, the EMA should also consider a more iterative guidance approach. The current process to generate scientific and procedural guidelines is extremely valuable as it allows for input from EU-wide expertise through public consultation and/or during workshops. However, due to the often-lengthy timelines of the process, finalising guidance may not be timely enough for some rapidly evolving regulatory areas. Therefore, an action for the EMA to consider would be for some guidelines to be supplemented by formal adaptive sections of guidance such as with a Q&A section that could evolve with more frequent updates. If implemented, this adaptable section would more quickly communicate new insights and learnings based upon advancing product experiences, academia/investigators' insights, patients'/clinicians' feedback, other regulators' changes, scientific advice results, product qualifications, stakeholder workshops, etc.
- Public workshops, publications, and participation in public-private partnerships or consortia allow this voice to be heard in a neutral setting to shape innovation in regulatory science and therapeutic areas.
- Consider how to rapidly share key learnings from this type of scientific advice with industry and other stakeholders in order to refine and improve the process as it moves forwards.
- We suggest creating more EMA guidelines of clinical investigation in particular fields as an additional action.
- It is important to link different engagement points for a more integrated and continuous dialogue, especially as the complexity of development increases with scientific and technological advances. It should also look to best leverage the expertise across the network.

- It is proposed to redesign a more flexible and integrated R&D product support mechanism, providing rolling advice across the life cycle of the medicines, including an opportunity for iterative CMC data submission during review of dossiers by relevant bodies.
- Integrate the opportunity for iterative CMC data submission during review.
- We also encourage EMA to build further on tailored scientific advice to support step-by-step development of new biosimilar medicine candidates as well as value added medicines with known active substances.
- Integrate the opportunity for iterative CMC data submission during review. This proposal can be achieved by delegation of advice and review of dossiers by relevant Working Parties (e.g. BWP for biologics, MSWP for M&S, Biostats WG).
- This enhancement of advice needs to integrate paediatrics in the development support provided by EMA, including clinical trials and scientific advice supporting licensing applications. Integrated advice also must include manufacturing as well. This could be achieved through enhanced dialogue with the EU PAT team.
- Within advice continuum, consider special perspectives for different types of products (e.g., ATMPs, paediatrics, drug-device combination products)

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

- A pilot could be used to better determine how to enhance support in a more holistic fashion for example by aiming for better linkage and dialogue between national CTA approvers and EMA -led scientific advice.
- Enhance the coordination of advice across EMA Committees, National Competent Authorities and other pertinent stakeholders. Ensure closer alignment of understanding between EMA and national regulators to minimise any conflict in views between centralised scientific advice and CTA assessment.
- Investigate possible IT solutions to facilitate the sharing of scientific advice documentation (briefing materials, meeting outcomes, minutes) easily across the EU regulatory network and with individual companies e.g. via a dedicated, confidential portal. This could be product-specific and would be added to during the lifecycle of the product.

1.4. Advance acceptance of digital endpoints

1.5. Facilitate translation of innovation via a re-engineered Innovation Task Force and synergy with an evolving EU-Innovation Network platform.

- The Innovation Task Force (ITF) that establishes a platform for early dialogue with applicants to identify scientific, legal and regulatory issues relating to emerging therapies and technologies, could enhance its role and be available for products later in development.
- ATMP developers need an agile, nimble, rapid approach to scientific advice which could be achieved under PRIME, through the ITF or other mechanisms.
- A more flexible system is also needed to support agile and quick development decisions. The ITF should be integrated into other advice platforms and advice on more general topics or concepts should be afforded.

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:

Underlying actions

1.1. Work with stakeholders to encourage complex collaborative clinical trials

- **Rename:** "Work with stakeholders to promote and facilitate the conduct of complex clinical trials"
- Work with stakeholders to encourage collaborative clinical trials
- Administrative processes must also be streamlined for innovation in clinical trials to be realized. For example, the process for amendments to ongoing clinical trials is long and arduous. Innovative trials designs may be of short enough length that delays to protocol amendments due to administrative processes could significantly impact the ability of the innovative trial design to add efficiency into the overall medicine development process.
- The current construct of CTA approval (using a 'per protocol' approach) does not lend itself to easily allow such designs to be implemented in practice… The current system for substantial amendments slows down clinical trials in the EU without providing benefits to patient safety as too many administrative amendments are categorized as "substantial"… Changing, or at least adapting, this paradigm therefore has the largest potential to fundamentally change the regulatory system and make it fit for the future. Failure to address this could mean that Europe becomes less attractive for clinical trials, especially as other countries are developing their clinical trial infrastructure, (e.g. China and S. Korea).
- It would be important for EMA to consider seamless clinical trials (where there is no step transition from Phase I to II to III). It is important to avoid a situation where seamless trials were possible in one regulatory jurisdiction but not in the other.
- The conduct of complex clinical trials potentially will be hampered by interpretation of the Clinical Trial Regulation such that parallel substantial amendments are precluded. Action to address this pragmatically would be beneficial.
- EMA/EC should ensure that the upcoming Clinical Trial Regulation is not preventing the advance of innovative designs (currently simultaneous amendments are impossible precluding use of innovative designs). The corresponding CTIS should also able to support innovative CT designs.

- We encourage the Agency to develop a new strategic initiative on Complex Innovative Clinical Trial Designs (including adaptive design and master protocols). Such initiative, ideally involving relevant stakeholders (developers, patients, clinicians, regulators, HTAs and payers) would: facilitate use and acceptability of such innovative clinical trial approaches, increase the regulators experience by allowing submission of case studies via a dedicated pilot programme and address different concerns from Regulatory Authorities (EMA and NCAs), Ethics Committees, HTAs. International collaboration with the FDA on the same matter would be beneficial, especially since such initiative is also ongoing there.
- It is critical if future clinical development is to be supported in the EU that there is broad acceptance of new clinical trial designs (e.g., master protocol: umbrella, basket, platform trials) by regulators and HTAs.
- Developing guidance on approaches such as the use of Bayesian methods for design and analysis, hierarchical modelling for borrowing historical control, synthetic control arms, etc.
- Optimise usage of CT information System. Consider how the data to be included in the CT Information System implementation can be better used across the EU Medicines Regulator Network so that national regulators have that full harmonised insight into the clinical data generated on a product during its development even when the clinical studies on the product are not being performed in that Member State.
- Initiate a pilot programme to facilitate broader discussion and about novel complex designs.
- Adopting a pragmatic approach to allowing parallel substantial modifications under the Clinical Trial Regulation, to facilitate operation of complex trials.
- Future ICH guidance on complex designs (when more experience is available).
- CCT multi-stakeholder workshops, demonstration projects (PPPs) and pilots to raise awareness, share case studies and identify best practise, and also to address challenges (e.g. concurrent multiple substantial modifications to CTs)
- Advance global coordination on the topic, for example via ICH deliberation on CCTs

1.2. Establish a multi-stakeholder, neutral, platform, to enable new approaches to clinical studies and to transform EU as a preferred location for innovative clinical research.

- Collaborate with international partners in ongoing initiatives such as the Clinical Trial Transformation Initiative and ICH.
- Advance global coordination on the topic.
- We would strongly encourage EMA to drive global multi-stakeholder discussion and alignment around CNS medicines development questions
- A pragmatic reflection starting from CTTI recommendations and their compliance with EU regulations is warranted. NCA, via CTFG, must be involved in this discussion, being the clinical trial a national mandate.
- Collaboration with CTFG to maintain innovation in the EU. Ensure upcoming CT regulation is not preventing advance of innovative designs (e.g. allowing parallel substantial modifications, as currently simultaneous amendments are impossible which precludes the use of innovative designs)

- Independent data analysis and trial pre-registration (registered report) and independent input into the trial design (or at least the ability to comment – e.g. expanded transparent scientific advice) should be pursued.
- Fulfilment of this objective requires strong engagement and alignment with the NCAs as responsible parties for reviewing and approving CTAs. Close collaboration with the CTFG is key to support clinical trial innovation and maintain competitiveness of the clinical trial environment in the EU.
- Increase collaboration between Member States' competent authorities and EMA in key scientific and regulatory aspects, in particular clinical trials. For example, GMO requirements remain an obstacle to the conduct of clinical trials in different countries. This forces developers to focus on few countries extending the time for completion of the development program.
- The EMA should endorse a patient-centric approach as opposed to a drug-centric approach.
- An improved understanding of the EMA's view and forward-looking aspiration for including patient insights and experience data in regulatory reviews and outcomes would enable more targeted investments in collecting such data for the benefit of public health.
- All stakeholders should work on defining patient centricity. We believe that patient centricity should ensure that the CT model adapts to the patient needs from a scientific and operational perspective for example allowing decentralised CTs using patient-centric endpoints.
- While we fully support the focus on fostering innovation in clinical trials as an important tool to facilitate medicines development across diagnostic categories, we encourage alignment between Agencies and welcome initiatives and guidance that is broadly applicable across therapeutic areas, both in an exploratory and confirmatory context. This in turn could help provide meaningful treatments for patients suffering from debilitating psychiatric symptoms or neurological disorders without restricting access to patients within a single diagnostic category.
- We also strongly support and encourage even more active EMA engagement in multi-stakeholder frameworks focused on endpoint development and usage to stimulate medicines development in brain diseases, such as for example the Critical Path for Parkinson's Consortium (CPP), as well as global regulatory engagement in platforms for discussion such as the Alzheimer's Association Research Roundtable.
- We support and encourage further EMA participation in multi-stakeholder efforts in this area, such as those conducted by the Critical Path for Parkinson's Consortium (CPP); Digital Drug Development (3DT) project which aims to obtain regulatory feedback on use of digital health technologies in Parkinson's disease clinical trials.
- Forum with HTAs and NCAs to facilitate better alignment in the clinical trial pathway with EU regulators
- Any such actions need to be aligned with the NCAs and should not be implemented without involvement of the NCAs.
- Use of opportunities for stakeholder interaction to share information on innovative trial designs, including aligned understanding of best practises, concerns and limitations will be valuable to ensure that this area continues to progress in the future.
- Facilitate better alignment between EU regulators and stakeholders in the clinical trial pathway.

- While discussion of innovative designs is an option via the Innovation Task Force, EMA could initiate a pilot programme that would allow for broader discussion and shared learning relating to novel designs.
- Support the organisation of high-quality clinical trials by participating in the training of clinical investigators and facilitating the transfer of knowledge to MS with fewer experience in conducting clinical research for regulatory purposes, as "applied regulatory science" programme. To this aim, the EU Network Training Centre for capacity building could certainly play an important role, as well as European Reference Networks.
- Regulatory bodies must work with academia and industry in defining the regulatory boundaries of these instruments. Along this line, the EU-PEARL project, an international collaborative action of more than 50 European organisations that under the umbrella of IMI want to create a common framework for the development of adaptative patient-centred platform trials will become a reference for the regulatory authorities to assess the efficacy of this instrument in the era of personalized medicine as a tool providing the innovation needed to efficiently evaluate modern treatments.
- EMA may be in a position to play a positive role with funders to support administrative aspects of clinical academic research such as database validation, file and record management, as well as play a role in moderation/proportionality through CTTI, ICH and Inspection Standards/expectations. Global collaboration (and if possible harmonisation) of expectations, guidance and standards will support delivery and trust in the data for this goal.
- Taking into consideration and complementing other ongoing EU activities e.g. IMI.

1.3. Drive adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance

1.3.1. Development pathways

- Consider a platform for information sharing like US FDA MID-3 (Model Informed Drug Discovery https://www.ema.europa.eu/en/documents/presentation/presentation-model-informed-drug-discovery-development-mid3-good-practice-use-prior-knowledge_en.pdf)
- The activities to advance innovation in clinical trials must be accompanied by a modernization of GCP.
- Clinical trials with GMO: supra-national review process (e.g. by the creation of an expert committee at EMA level)
- Given the increase in ATMPs, particularly in the area of Rare Disease, the development of innovative trial designs to accommodate the development of treatments such as gene therapy will be key in delivering new therapeutic treatments in a timely manner.
- It is important for the innovation to be cascaded down into the regulatory approval system for CTAs and ensure that there is consistency in the decision making.
- 'Novel practices' should include integrated assessment of 'therapeutic pathway'* as part of treatment strategies (*continuous monitoring drug from administration through pharmacological activity and pathophysiological modification, to impact on disease/symptoms)
- The proposed adaptive approaches for iterative development result in a risk shift from pre-marketing to post-marketing. This may result in a greater population under risk instead of the

intended risk minimisation. Speedy access in populations of urgent need should not be a standalone aim without taking effectiveness/efficacy and safety into account.

- This section focuses on innovation of trial designs and methods but should also pay attention to innovation of drug development strategies. In this way, drug registration will continue to be based on the 'confirmation' of efficacy and safety in randomized clinical trials of sufficient size and quality, albeit with novel designs and methods. Individual studies in the drug development process are still insufficiently integrated to provide 'totality of evidence'. -EMA should promote the generation of information about each step of the 'therapeutic pathway' (connecting exposure and pathophysiology to clinical effect) in basically every study during all phases of development.
- EMA should demand that the mechanism of action is explained and informs each stage of the drug development pathway.

1.3.2. Digital

- We support the proposal to develop capability to analyse individual patient data. This can help flag information that has not been adequately captured in clinical study reports.
- Collect RWD during trial to identify clinical features of patients
- Reflect on scope and quality criteria of RWD; Should be cautious using this data to establish clinical effectiveness due to high confounding…while RWD can be used to characterise the patient population in clinical practice or to collect data on resource use it is hardly possible to generate robust data on treatment effects unless these effects are very large….should be cautious using this data to establish clinical effectiveness due to high confounding
- In in silico clinical trials, 'virtual' patients would be given a 'virtual' treatment, enabling us to observe through a computer simulation how the product performs and whether it produces the intended effect, without inducing adverse effects that might be potentially dangerous for the patient. We believe that such in silico clinical trial could help to reduce, refine, and partially replace real clinical trials.
- Modelling and simulation and extrapolation in clinical trials e.g. in silico trials, needs to incorporate RWD, natural history, and/or observational data.
- Advance acceptance of digital endpoints.

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

1.4.1. Endpoints

- Develop guideline for Biomarkers qualification.
- Surrogate outcomes cannot be accepted, unless they have been validated as predicting patient relevant outcomes. Moreover, the use of surrogate endpoints should be discouraged nor accepted where final outcomes are achievable within a reasonable timeframe and without harm for trial participants.
- Consideration should be given to the practical application of the orphan drug regulation when addressing tissue agnostic indications.
- Due to the limitations of outcome measures in prodromal and pre-clinical phases of neurodegenerative diseases, we advocate for further discussion and global regulatory alignment on

uses of for example integrated endpoint approaches, where combined data on several mutually supportive outcome measures can be interpreted as supporting efficacy as suggested for example in the draft FDA AD guidance.

- Engage with patient organisations e.g. when developing novel endpoints.
- Develop guideline for Patient Reported Outcome Development of PRO in Europe is very uncertain and only in few cases are data allowed in the product label.
- Allow decentralised CTs using patient-centric endpoints
- One important component of innovative clinical trials is the betterment of endpoints and the identification of surrogate endpoints that allow for shorter duration trials to provide meaningful insight into long term outcomes. Questions remain as to how surrogate endpoints should be adequately validated in order to be used in clinical trials. EMA could consider publication of evidentiary considerations for the development of surrogate endpoint markers.
- Revising clinical guidelines to allow for new endpoints associated with digital technology.
- Post-approval studies should be designed around clear endpoints and objectives and within a defined timeframe to address uncertainties during MA

1.4.2. RCTs

- The EMA has the opportunity, e.g. through its regulatory guidelines, to push the methodology of pivotal randomised controlled trials toward a pragmatic approach. The Agency could request that one of the two randomised controlled trials for approval adopts a pragmatic design and, possibly, is conducted by an independent party.
- Innovation in clinical trials is a vague concept. Up until now, many so-called modern trial designs have been discussed, but methodological problems that result in a high susceptibility for bias have not yet been solved. Thus, they need to be regarded as being acceptable for explorative trials only.
- As a normal rule, the gold standard of genuine comparative randomised clinical trials would be a key element for "improving the scientific quality of evaluation" but is sadly absent of EMA's strategy. We also call on EMA to design precise guidelines outlining these standards for particular evidence requested. The service "à la carte" through early scientific advice should be limited to exceptional situations.
- Demand whenever possible for pre-approval studies 2 comparative clinical trials, using clinically relevant comparator (standard treatment), clinical/patient relevant outcomes and relevant target population (e.g. older people)
- We invite EMA to raise the bar with strong evidence requirements for marketing approval including comparative trials against standard of care treatment (whenever possible), using clinically relevant endpoints including quality of life and overall survival.
- New clinical trial designs are needed to respond to the new patient needs. To this end, it is important to strengthen the scientific rigour and relevance of RCT's used in the marketing authorisation process. Large simple RCTs in the later phase of development should be supported to collect meaningful data on the patient groups that will be treated in clinical practice. Gender differences and other relevant subgroups (such as the elderly) must be reflected in RCT. In order to improve trust in the EU regulatory system, it could be envisaged to a) demand comparative RCTs where possible, b) require that one of the 2 RCTs for approval be done by an independent party, c) pool resources across Member States to do meaningful-pragmatic RCTs responding to the

right questions of clinical practice, d) require superiority trial whenever possible rather than non-inferiority trial.

- Increase the representativeness and include over 65s in RCTs

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:

Underlying actions

1.1. Develop methodology to incorporate clinical care data sources in regulatory decision-making

- Before developing methodologies to incorporate big data, it should be made clear under which circumstances, for which products (pharmaceuticals in vitro diagnostics vs. Borderline products) and for which purposes this kind of data can and will be used in regulatory decisions
- A critical reflection on which data is relevant in the context of drug development processes needs to be undertaken.
- Again, begin with some disruptive products to set up the roadmaps. AI and digitalized medicine is the big trend in clinical decision making. Large data, digital data are way more valuable in medicine than controlled, small sample size trials. The key is the quality of the large data analyses. In regulatory, encourage the use of large data and apply the appropriate method is critical.
- A clear framework for how digital measures can provide meaningful insight into medicine development is key. Digital devices can also generate extremely large data sets. Thus, important consideration must be given for the interpretation and analysis of this data.
- However, it will be very relevant to address also potential advantages of new data sources. For example, in clinical trials, the exploration of novel methods of self-measurements by patients can be supportive, as long as they represent patient relevant outcomes.
- Please also consider that evidence based on data collected in 'real-world' circumstances, may also have a large public impact. It is important to also consider the potential consequences for society, if data from mobile and wearable technologies are accepted for drug registration. If a 'disease outcome' is based on data that every individual can collect on their own smart phone, this may lead to unforeseen changes in self-diagnosis, new perceptions of 'health' and 'disease' and changes in behaviour and health care policies.

- More EMA transparency on acceptability of novel approaches.
- We would encourage the EMA to also explore the use of real-world endpoints in regulatory decision making, including outlining the acceptability of real-world endpoints for specific contexts of use and description of a framework for validating these endpoints.
- A clear framework on how to handle and incorporate these types of data into regulatory decision making is needed. Action on this in the shorter term could also potentially help with alignment across major regulators on key issues e.g. the proposals in the 2018 FDA draft regulatory framework for drug-related software. It will be important to ensure that there is a co-ordinated and consistent approach to the handling of these types of data across the EU regulatory network.

1.2. Modernise the GCP regulatory oversight to enable decentralised models of clinical trials coupled with direct digital data accrual

- We strongly agree with the action to modernise GCP regulatory oversight. Modernisation of GCP regulatory oversight must consider technological advancements. For instance, a truly virtual or decentralized trial would require use of technologies such digital signatures, which are currently inconsistently accepted by Member States.
- Define which quality standards have to be fulfilled to incorporate such data into regulatory decision-making.
- Advancing acceptance of digital endpoints: As part of the development of a regulatory framework for emerging clinical data generation, we propose progressing a platform to gain multi-stakeholder input on digital endpoints. The current processes may be lengthy which is not adapted to the agility sponsors need when determining a CT design.

1.3. Develop the capability to assess complex datasets captured by technology such as wearables

- Introduction of/piloting alternative mechanism to manage large submissions e.g. cloud submissions.
- Training sessions on digital technologies (i.e. artificial intelligence, Big Data, virtual clinical trial, sensor generated data) represent an important opportunity for the experts working in the European regulatory agencies. Nonetheless, due to the complexity of those technologies, training may not be sufficient and the involvement of different professionals (i.e. information engineers and data scientists) is required. It could be an opportunity for the EMA to establish a multidisciplinary working party dedicated to the application of digital technologies to drug development, authorization and post- marketing surveillance.
- We strongly agree with developing the capability to assess complex datasets captured by technology such as wearables.

1.4. Facilitate training and understanding of healthcare professionals and patients to access and participate effectively in such trials.

- Educate healthcare professionals on 'precision medicine' (mechanism-guided drug/patient matching, dose optimization and monitoring)

1.5. NEW! Clarify questions on data ownership and data security

- Need for validity and reliability to be demonstrated and guidelines for GDPR compliance.

- To ensure data privacy we need validated, automated de-identification systems. And advanced consent.
- There is a need to clarify the responsibility of ownership and data security, as well as how to make it open for research.
- Questions related to data protection and data ownership need to be addressed as well.
- There is a need to better understand the ownership of these data collected and who are the authorities safeguarding the correct use as well as mechanism of storage of the data repository. It is also important to consider the option of OPEN data for the transparency of the research process and the researcher.
- Further dialogue with regulators globally on how to utilise technology enabled objective assessment of cognition, behaviour and functioning in CNS trials, as well as stakeholder alignment regarding privacy/GDPR considerations when utilising DHTs such as those meant for passive monitoring.

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:

Underlying actions

1.1. Expand the benefit-risk assessment by incorporating patient preferences

- When patient preferences are increasingly incorporated it has to be ensured that this is done in a transparent and impartial way with clear rules for conflict of interest.
- How will patient preferences be used in regulatory decisions making? For instance:
  - Are preferences intended to help regulators interpret clinical trial outputs directly, or provide a broader patient-centred benefit risk assessment? Or will patient preferences inform risk management strategies?
  - How will preferences influence decisions? For instance, if patients are willing to tolerate treatment risks for its benefits, is that sufficient for product approval?
  - Given the answer to these questions, for which decisions are patient preference data helpful? Which decisions are likely to be preference-sensitive?
- How would patient preferences interact with structured decision making? This partly depends on what is meant by structured decision making, and it will be important to be clear about this. Assuming this means structuring committee discussions and decisions, and perhaps even performing a quantitative benefit-risk assessment with committee preference data, how would committee and patient preferences both be incorporated into the benefit risk assessment? If they conflict, how should this be resolved?
- Guidance on methods - How can quality be assured? It will be important for the EMA to provide guidance on how to deliver on an expanded BRA, and to consider how the quality of this work is assured.
  - There are many preference and structured decision-making methods that could be applied to support an expanded BRA. It will be important to provide guidance on which methods are considered appropriate. This should consider the particular use to which the EMA intends to put such methods. It will also be important to provide guidance on how these methods should be implemented.

- In this endeavour it is important the EMA consider and build on existing good practice guidance (such as that issued by ISPOR), guidance provided by the FDA, and the results of IMI PREFER. Given the subjective nature of preferences, and the potential biases that need to be considered when conducting preference research, there may some scepticism about the rigor of the preference data used in the expanded BRA. It will be important for the EMA to consider how best to assure quality. For instance: sponsors could be asked to publish protocols, a process could be established to provide scientific

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

- Effects tables are often insufficient to render a B-R decision. A structured approach for the assessment, (not tabulation of key B-R data), is needed. This should be suitable for sponsor use and not be a regulators' communication tool, as currently.
- Behavioural change approaches would be welcome to be explored as well as the use the Brass model as they may be valuable to the B: R evaluation of non-prescription medicines.
- How to ensure consistency; Importance of favourable and unfavourable effects… However, we also realize that this section is not always formulated in the same way.
- A deepened discussion about unmet medical need, severity of disease, existing treatment options and the size/amplitude in effectiveness in absolute terms would be very positive.
- How to improve 'health literacy' is not explicitly addressed here, we believe it underpins the actions to incorporate patient preferences and individual data in the benefit-risk assessment as well as the communication efforts of these assessments to patients, HTA bodies, payers and the general public.

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

- Any plans to (re-)analyse clinic trials individual patient data is associated with high investment within the regulatory network.
- Possible/potential roles of NCA's assessments capacities in this context would need to be explored in a timely manner
- Develop the capability to analyse individual Patient Data to support decision-making, we consider that this is not the best use of the regulator's resources. EMA should focus on understanding and reviewing the Individual Patient Data but not re-analysing data in-house.

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

1.5. Enhance structured benefit/risk assessment to improve communication to the public

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

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:

Underlying actions

1.1. Enhance modelling and simulation and extrapolation use across the product lifecycle and leverage the outcome of EU projects

- While there is disagreement on the absolute values, all experts agree that the cost to develop and bring to market a new medical product has been raising exponentially in the last 30 years. In every other industrial sector this problem has been solved by adopting and widely deploying modelling and simulation. It is time we pursue the same revolution for medical products. If computer models can guide the diagnostic, prognostic, or therapeutic decision for individual patients, why should they not be able to advise on the safety and efficacy of new medical products? Thus, the safe adoption of In Silico Trials should be at the core of the EMA strategy, and not only in connection with the reduction of animal experimentation.
- The topic of 'Optimising Capabilities in Modelling, Simulation and Extrapolation' is considered of high importance as currently regulators rely on 'actual data', often generated in real time, and are reluctant to accept alternative approaches to provision of evidence during development. Thus, increasing acceptance of predictive approaches, based on modelling, simulation and extrapolation will advance the clinical development of medicines and acceptance of models in the non-clinical and CMC / Quality fields will also add value.
- Increasing acceptance of predictive approaches, based on modelling, simulation and extrapolation will bring advances in the quality, non-clinical and clinical fields. For example, in the CMC area, process modelling of the manufacturing process could be used to support development and scale-up, and to set up the control strategy.
- The CMC and Quality fields are a rich source of scientific and innovative approaches using M&S and prediction that could be utilised.
- In particular, the CMC / Quality arena is a rich field of scientific and innovative approaches using modelling, simulation and prediction that could be utilised, for example
  - Stability modelling and prediction of degradation

  - P modelling to support bioequivalence evaluation
  - Process modelling (e.g. development of a digital twin) of a manufacturing process (drug substance and/or drug product) to support development and scale up and control strategy development
  - Models built from prior knowledge that can support post-approval and the setting of clinically relevant specifications
- Predictive and modelled approaches to safety evaluation (for active substances, impurities and manufacturing intermediates) that minimise animal utilisation is a current field of interest that demands further investment and acceptance (e.g., the EMA Reflection Paper on Qualification approaches for non-mutagenic impurities).
- Highlight the importance of advancing the recognition of extrapolation in a paediatric patient population in CNS.
- Accepting modelling (and surrogate) endpoints for clinically relevant outcomes measures.
- M&S use in longitudinal dose response analyses in Phase 2 trials; use within adaptive designs, etc.
- Use disease modelling to support clinical relevance of treatment and long-term value demonstration in brain disorders

1.2. Promote development and international harmonisation of methods and standards via a multi-stakeholder platform

- Finally, as advances in MS, including machine learning and AI, continue, EMA must provide guidance for the inclusion of advanced models into drug development. EMA must also effectively educate industry and academic stakeholders engaged in MS for drug development to ensure tools are developed according to the standards set by EMA.
- Collaborating more with other regulatory authorities regarding acceptance of innovative approaches.

1.3. Increase capability and redesign the operations of relevant working parties to ensure wider knowledge exchange.

- There is a need to invest in Centres of Excellence in Regulatory science at an EU level, to work with regulatory agencies to provide training and research on Modelling & Simulation tools (i.e. PBPK models).
- Modelling/Simulation and Extrapolation require a culture change and a new interdisciplinary operational model. These tools should however not be left at the hands of mathematicians at risk of having patients and clinicians losing trust in regulatory decision-making that they might not understand or control, but rather integrated these tools in the clinical decision making by educating and adapting them to the clinicians need. Extrapolation will remain a clinical decision, particularly in areas when you don't have enough data to develop models and statistical approach, with still benefit-risk balance decision to be made. Having quantitative experts in all the EMA committees and their respective EMA teams to bridge with the quantitative working parties would be already a great asset. Otherwise quantitative tools will never be integrated in regulatory decision to their full potential.
- Increased EMA network expertise in applying M&S and evaluating/interpreting M&S results.
- Collaborating more with other partners e.g. IMI.

1.4. NEW! Data sharing

- Off-patent medicines could be a learning opportunity on gathering evidence through real-life use data and modelling, simulation and extrapolation

1.5. NEW! Artificial intelligence (AI)

- As advances in MS, including machine learning and AI, continue, EMA must provide guidance for the inclusion of advanced models into drug development. EMA must also effectively educate industry and academic stakeholders engaged in MS for drug development to ensure tools are developed according to the standards set by EMA.

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:

Underlying actions

1.1. Ensure the evidence needed by HTAs and payers is incorporated early in drug development plans, including requirements for post-licensing evidence generation

- Strengthen parallel EMA/HTA scientific advice to reduce risk of inadequate information provided to EMA/HTA at time of evaluation; EUnetHTA can be used as a platform to exchange information between CHMP and HTA; allow HTA assessors to have this information in parallel to CHMP evaluation (multiple)
- Collaborate with HTA bodies on post-authorisation evidence requirements and introduce EU clinical registries post-authorisation in addition to existing managed entry agreements; this could supplement the means to address uncertain evidence (small, single-arm, or single-centre, early phase clinical trials) from emerging cell and gene therapies; this uncertainty affects following reimbursement issues: estimates of incremental costs, health benefits and the decisions made about implementation of these therapies; clinical registries would provide highly structured clinical data to healthcare professionals on safety and effectiveness, and can be used to compare the effectiveness of different treatments for the same disease or condition.
- EMA support for aligning priorities for post-marketing activities would be welcome. Post-marketing activities are mostly PASS and sometimes long-term efficacy. HTA requirements include long-term efficacy, quality of life (QoL), activities of daily living (ADL), data in specific age groups, subgroups and biomarkers. Data quality e.g. if gathered using wearables is an additional important consideration.
- There needs to be a continued dialogue on what evidence is necessary in the post-marketing setting. In situations where the EMA and HTA are not fully aligned on post approval data requirements, dialogue to agree on the appropriateness of measures to follow-up is useful for HTA. This would be particularly useful where evolving knowledge during development suggests a different endpoint or way of monitoring would be more appropriate in the post-marketing setting than utilised in clinical trials.

- A sustained therapeutic effect is anticipated with many future ATMPs and determination of the extent of durability will only be possible with long-term post-marketing follow-up.

1.2. Enable information exchange with HTAs to support bridging from benefit-risk to relative effectiveness assessment

- It could be useful to invite HTA experts to CHMP discussions for issues that are known to be a cause of difficulties for the downstream decision-making. The same applies to technical guidelines, where EMA and HTA bodies develop different sets of guidelines on the same topics, which can result in counter-productive divergences.
- Differences between HTA and EMA assessments are justified and do not hinder better cooperation; however, the differences should be better explained in the public domain

1.3. Discuss with HTAs guidance and methodologies for evidence generation and review

- The inclusion of core outcome sets (COS) throughout the ecosystem from regulatory to HTA assessments
- The strategy acknowledges the importance of discussing (we would prefer the term "co-creating") with HTA bodies, guidance and methodologies for evidence generation and review. Along this line, specific programs for HTA assessment in the field of ATMPs should be developed and implemented. Impact assessment should also be developed in routine evaluations of benefit-risk.
- Conduct an EMA/EUnetHTA workshop dedicated to ATMPs
- However, we believe that due to specific features typically associated with brain disorders it is critical that a framework for evaluating long term value, specifically in CNS medicines, is developed and endorsed across stakeholders.
- Guidelines on how to involve the patient in the process again would be helpful (Data collection, defining the research question, value to patient, dissemination of results etc.)
- EMA should drive open dialogue with regulators, HTA bodies, payers and relevant stakeholders to align on acceptable ways to: Use disease modelling to support clinical relevance of treatment and long-term value demonstration in brain disorders; Monitor patients long term in routine care in a cost-effective manner for value demonstration

1.4. Contribute to the identification of priorities for HTA

- The EMA could also ensure coordination between the various horizon scanning activities such as the International Coalition of Medicines Regulatory Authorities (ICMRA) strategic initiative on innovation and the International Horizon Scanning Initiative (IHSI) initiated by Beneluxa (grouping together HTA and payers from some EU countries) to help HTA and payers identify what and when disruptive technologies could be made available.
- Ensure HTA involvement for PRIME designation to including a cross check for the unmet medical need.

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

- When monitoring the impact of decision-maker engagement, target parameters should be defined. While discussion often focusses on access alone, in reality, the triangle of access, affordability and added benefit is relevant.

1.6. NEW! Further develop the structured interaction between EMA and HTA bodies, respecting the respective remits

- Proposal to reflect on establish a permanent working structure and information exchange process with EMA and HTA bodies/payers, with relevant objectives, planning and responsibilities
- Describe more clearly the proposed involvement plan with stakeholders (timelines, operational approach)
- Increase clarity specifically on cooperation with HTA bodies

Bridge from evaluation to access through collaboration with payers

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

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:

Underlying actions

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

- The current FDA initiative to establish core, co-created sets of clinical outcome assessment and related end points is a good example of helping to define a common ground that reflects the patient perspective and which informs the whole lifecycle of medicine.
- Create a mechanism for early and frequent stakeholder involvement—between regulators, payers, and the manufacturer—in a safe harbor environment to determine unmet medical need and the information needed in a clinical trial and/or RWE study.
- More specifically, as the recipient of feedback from both payers and regulators, Industry stakeholders would likely have important insights on the challenges of the current processes, and could assist the Agency by providing input or advise on potential strategies to address or mitigate them.

1.2. Contribute to the preparedness of healthcare systems by creating opportunities for collaboration on horizon scanning

- In our opinion, a robust horizon scanning system at national (and European) level could help decision-makers to plan and prepare for innovation. Cooperation and exchange of information between EMA and HTA/payers in the field of horizon scanning, including timely sharing of information regarding upcoming regulatory submissions should be envisaged, in order to impact on Health Care Systems' preparedness

1.3. Clarify the treatment-eligible patient population included in the labelling, and its scientific rationale

- Rename underlying action as "Consider more structured interaction between EMA and payers, respecting the respective remits"
- Clarify the treatment-eligible patient population included in the labelling, and its scientific rationale
- We suggest EMA to start a reflection on establish a permanent working structure between EMA and payers with relevant objectives, planning and responsibilities.
- Identify opportunities to avoid duplicative efforts between EMA and its HTA/payer partners; and,

1.4. NEW! Participate in discussions clarifying the concept of unmet medical need

- There are benefits to engage with payers earlier to gain insight into their perspectives on unmet needs and priorities. Early engagement also helps to prepare payers for potential major impacts from breakthrough innovation.

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.

Underlying actions

We believe EMA needs to go far beyond and suggest reframing as "ensuring the patient voice is systematically incorporated throughout drug development & associated evidence generation"

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

- Seek agreement on how and where to include patient experience/preference data in regulatory submissions and labelling - support multi-stakeholder agreement on a framework for evaluation of patient preference data
- Define expectations for scientific rigour i.e. what constitutes the scientific standard -drive understanding across stakeholders of what constitutes patient experience data, where the data can take many forms: feedback from focus group, interviews, blogs, etc.
- Develop with EMA relevant patient centred QoL measurement tools; Patient input into long term side effect and QoL. Involvement of patients in PRO validation. EMA to address lack of standardisation and of perceived lack of rigour, with subjective data and varying levels of understanding among reviewers
- EMA should be encouraged to take a more vigorous approach to the whole issue of patient-focused drug development. Patient perception of value should rightfully be reflected in the SmPC.
- Embedding patient priorities into clinical trials design, via clear EMA guidance co-developed with patients, is needed to ensure that meaningful data is generated for regulatory assessment.
- Data from treatment optimisation studies, registries, observational clinical trials and electronic health records of patients should be interlinked and embedded into decision making process.
- Reinforcing the need for patient preference elicitation: IMI PREFER believes that CHMP and EUnetHTA's opinion on the acceptability of such a framework and the DCE (Discrete Choice Experiments) method can promote the broader use of patient preference studies in research and development and evaluation of novel treatments and ultimately result in the development of dedicated guidance.
- Multi-stakeholder agreement on a framework for evaluation of patient preference data

  - RWD should include patient-generated data
- Evidence to demonstrate added therapeutic value – at time of MA evidence relevant for HCPs and HTA/payers, request clinically relevant endpoints e.g. OS
- EMA to build on existing framework for stakeholder engagement, including patients and HCPs
- EMA should strongly encourage and set clear expectations towards applicants by insisting to involve patients in the studies that are being submitted; this by insisting on patient engagement on the content creation of the submission. E.g.
  - Update guidelines to require patient systematic involvement
  - that every study evaluates the need for PROs that are being tested for relevance by patients and ease of use
  - a justification that every outcome studied is relevant to patients based on qualified and quantified views (not just by doctors)
  - make explicit that there is no opportunity to develop submissions to ask for patient engagement; e.g. EMA could clearly state that they expect documentation of the fact that patients have been involved in design, implementation and interpretation of pivotal studies

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

- Qualification of PROs: the current qualification procedure is too lengthy to fit the pace of development. Best practice guides on high-quality PRO trial tools would help to ensure that patients' voices are central to informing shared decision-making, labelling claims, clinical guidelines, and health policy and making patient-centred care a reality
- A clinical outcome, reported by a clinician, carer or observer could be equally relevant to a patient.
- A coordinated approach to PROs across therapeutic areas and a proactive update by the EMA of specific clinical guidelines on these would be welcomed. enhance international collaboration with regulators in ongoing initiatives, notably with regulators that are pioneering several initiatives on patient-focused drug development such as the US FDA.
- Welcomed a core health-related quality-of-life PRO but questioned whether a set of PROs would be more appropriate across disease areas.
- Minimum standards for the development of core outcome sets (COS). We suggest that clinical guidelines should be updated to include not just reference to inclusion of a PRO (where PRO would be better phrased as 'Patient Relevant Outcome'), but to include reference to the inclusion of a COS when a relevant COS exists.
- With a view of fostering effective use of PROs in decision making, it will be particularly important for EMA:
  - to address the lack of standardization and the perceived lack of rigor associated with "subjective data", and varying levels of understanding of this type of evidence among reviewers;
  - to foster interactions with industry and other stakeholders and provide transparency on how related data is assessed and rated;

  - to consider aspects linked to digital health (tools, endpoints etc.);
  - to consider early the perspectives of HTA.
- EMA guidance co-developed with patients to include patient priorities in CTs and PROs ; Put PROs and patient preference studies top of the list Consult HCPs and patients to identify outcomes to be measured in clinical research ;Clarify if one core PRO or a set of PROs – compare across diseases.; Coordinated approach across therapeutic areas; Patient centred outcomes not only PROs – also reported by clinician not just patient; A HQoL PRO, may not require the development of a new tool, several tools are already available.
- Deliver the inclusion of PROs in collaboration with other stakeholders, particularly HTAs, and in consideration of aspects linked to digital health

1.3. While validating PROs, address patients' needs and leverage patients' expertise

- Leverage patient-reported outcomes in diseases where the disease itself may impair the ability of the patient to self-report, such as neurodegenerative diseases or schizophrenia
- Rare diseases: validating PRO tools may not be straightforward due to rarity of condition
- Paediatric outcomes reported by their caregivers and a focus on special patient populations are also essential to advance development
- The inclusion of patient important outcomes through the uptake of core outcome sets (an agreed minimum set of outcomes that should be measured and reported) throughout the ecosystem. A well-developed core outcome set will have included all relevant stakeholders, including patients or their representatives, in the determination of the most important outcomes to be measured.
- EMA perspectives on PROs are quite conservative:
  - Patient perception of value to be reflected in SmPC;
  - More transparency on how EMA uses patient preference information for B/R assessment and orphan designation
  - EMA should address the lack of standardisation and perceived rigor in "subjective" PROs.

1.4. Enhance patient involvement in EMA scientific committees

- It is important to ensure contribution from smaller patient organisations and allow them to contribute independently of umbrella organisations.
- Stakeholder input to be well-documented in EPAR;
- Update guidelines to require patient systematic involvement
- We recommend introducing the concept "co-creation" when patients are involved in the decision-making process as they become transformative agents of the process.

1.5. 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

- Real challenge is the sensitivity of the measure. Before developing a new tool, there should be efforts towards consensus building on the appropriate tools across all stakeholders

- It isn't clear what the need for the development of a new health related quality of life tool is or why the EMA considers this important. There are several tools available and it is also a field where considerable research is in progress. It is good that the proposal is to co-develop this with HTA agencies, but any such work should start with a review of the need.
- Co-development of a core health-related quality-of-life PRO with HTAs is supported, but it is not clear if the proposal is ONE core PRO along with HTAs, or core SET of measures. We suggest considering how robust/meaningful the comparison is e.g. across different diseases.
- In developing core HQoL PROs, the Agency should work with stakeholders to identify tools which have the appropriate sensitivity and representativeness, even in cases of rare diseases.
- Discrete Choice Experiments can be used on top of PROs
- Welcomed a core health-related quality-of-life PRO but questioned whether a set of PROs would be more appropriate across disease areas.

1.6. NEW! Drive global alignment on the scientific methodology to gather patient contribution to drug development New core recommendation no.6

- EMA works closely with the FDA on this initiative to ensure a global approach. The output from the existing cluster group should be more transparent to industry.
- The key questions are how to determine what is relevant to patients, how to measure it and how to ensure a consistent understanding of how various stakeholders will evaluate it. There has been recent guidance from both WHO and FDA on gathering patient input and future guidance is expected from IMI-PREFER and CIOMS. Patients in the EU need EMA to support key EU initiatives like IMI PREFER, IMI PARADIGM & EUPATI whilst at minimum keeping pace with initiatives in other regions
- Work with FDA to ensure a global approach – output from existing cluster more transparent to industry Drive global alignment on scientific methodology to gather patient contribution
- In the approach to development, alignment and implementation of guidance for capturing patient insights for file submission and leveraging insights from initiatives such as the development of Clinical Outcome Assessment (COA) guidance by the FDA.

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

Underlying actions

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

- Build on ongoing efforts (in EU and internationally) to provide clarity on scope and quality of sources of RWE, recognising governance and resources required for these sources and identifying where gaps exist. The EMA and HMA could also partner with the European Commission to develop a unified approach on the collection, curation and interoperability of health data and establishment of a European health data resource base for the benefit of European citizens.
- Promote adoption of a common data platform.
- Demonstration projects are essential to increase knowledge, capacity and confidence levels amongst RWD stakeholders including pharmaceutical companies and regulators. Piloted approaches are also ongoing in other countries and regions (3), and EMA should remain active in this field of research internationally. Moreover, enhanced acceptability of RWD to support regulatory decisions must also involve and evolve with patients, HTA bodies, healthcare professionals and other stakeholders.

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

- The EMA RSS 2025 also includes an objective to "develop a capacity that will enable the Agency to rapidly and securely access and analyse large amounts of healthcare data". It is recommended that such a capacity (e.g., system or algorithm) should be developed in consultation with relevant stakeholders including industry.
- Includes building computing capacity to receive, manage and analyse large data sets including patient level data (PLD); establishing a federated network of analytics centres linked to regulatory agencies; strengthened Scientific Advice that can receive PLD, and; the Network ability to validate AI algorithms.

- The EMA should perform statistical analysis in house on raw data while ensuring the independence and integrity of the process. Such analyses should be available to 3rd parties

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

- Edit: **"Start an initiative where the regulatory system learns based on submissions of big data (including RWD): to include submissions from industry through the product lifecycle, tracked for outcome and learnings shared with stakeholders and the development of guidance"** (Includes a 'big data learnings initiative' where submissions that include big data are tracked and outcomes reviewed so that leanings can be fed into reflection papers and guidelines. Also, guidelines on study conduct and reporting, enhancement of the existing EU PAS register to increase transparency on study methods)
- Launch a strategic initiative to integrate RWE in drug development, including the use of demonstrator projects to engender familiarity. This initiative should assimilate building blocks across the commonly available regulatory tools (e.g., guidance, pilots, capability building, stakeholder engagements):
- Introduce a pilot programme for RWE case studies to explore how RWD can be better incorporated into decision making stakeholders.
- A dedicated EMA RWE pilot program in which regulators and sponsors can publicly share lessons learned (with protections for confidential commercial information) for the benefit of all stakeholders, which will improve the quality of RWE submissions in the future (note: further suggestions for public workshops below).
- Consider a pilot programme for RWE case studies to explore how RWD can be better incorporated into stakeholder decision making. This should include considering the possibility of more frequent EMA interaction on study design, etc., in order to facilitate shared learning.

1.4. NEW! Establish an EU Data Quality and representativeness framework

- To include guidelines, a data standardisation strategy, a strengthened process for Scientific Advice data qualification, and promotion across the Member States of uptake of electronic health records, data linkage and secure data availability.
- The development of novel means to answer important questions regarding the quality of RWD, and therefore its ability to generate quality RWE, is essential. Further, guidance documents from regulatory agencies directing stakeholders who engage in this task will facilitate the generation of RWE from retrospective RWD and should be emphasized.
- Build on ongoing efforts (in EU and internationally) to provide clarity on scope and quality of sources of RWE, recognising governance and resources required for these sources and identifying where gaps exist. The EMA and HMA could also partner with the European Commission to develop a unified approach on the collection, curation and interoperability of health data and establishment of a European health data resource base for the benefit of European citizens.
- To ensure "high quality" RWD, internationally aligned fit-for-purpose quality requirements for regulatory purposes are essential. Beyond standards, however, this discipline also needs quality management in practices related to creating and using RWE sources. Establishing best practice in quality management will also need pilots to advance practice. This could include both retrospective

studies, as well as prospective case studies. The methodologies must enable EMA to trust RWE without having to re-do the analyses themselves.

1.5. NEW! Ensure the EU Regulatory network has the expertise to regulate product dossiers including real world data

- Includes: development of a Big Data training curriculum and strategy based on a skills analysis across the Network; deliver collaboration with external experts including in academia, and; targeted recruitment including data science, biostatistics, epidemiology, advanced analytics and AI + strengthen EMA working groups with new expertise on real world data.
- Expertise Continuing education resources to enhance reviewers' consistent understanding of novel RWD source types, RWD quality considerations, and evolving analytical methodologies for generating RWE (especially methods applied to observational data).
- Expertise Steps to ensure consistency in how RWD and RWE approaches are evaluated by EMA and national competent authorities. For example, FDA has established a "RWE Subcommittee" to bring about greater consistency across the agency's different review divisions.

1.6. NEW! Collaborate with stakeholders in Europe and internationally to leverage ongoing initiatives and share best practice on RWE

- (includes development of guidelines at multilateral for a such as ICH; contribution to data standards through standards bodies; bilateral collaboration and sharing of best practice with international partners + Establish an EU big data 'stakeholder engagement platform').
- Collaborate with regulatory authorities in other regions as well as other stakeholders to facilitate the development of harmonised approaches (where appropriate) in the future.
- Further advance the global regulatory discussion on the place of non-randomised trial designs and data, with the aim of enabling more efficient medicines development without negatively impacting the foundation for B:R assessment
- EMA is encouraged to work globally to align with other regulators and especially the US FDA. Importantly, data standards should be agreed internationally.
- EMA/EC are encouraged to organize fora to align on design, collection and use of RWD with regulators and HTAs
- The Big Data taskforce should have a more open and inclusive approach: of the five key recommendations of the report regarding data (standardisation, quality, sharing and access, linkage and integration and analytics), some are listed as being owned by regulators while others have a common ownership. In practice, input from a wider range of stakeholders (HTAs, patients and consortia) with expertise would be beneficial in all aspects. https://www.ema.europa.eu/en/documents/minutes/hma/ema-joint-task-force-big-data-summary-report_en.pdf
- Coordinate workshops to progress dialogue and publish workshop conclusions. The impact of healthcare RWE is system wide. To move this innovative agenda forward, regulators, industry and other stakeholders need to engage widely to help establish momentum for appropriate use of RWE. Workshops are one mechanism that has worked in other domains for regulatory change and could be used for this purpose. These workshops would be used to advance standards and best practices, build consensus and, encourage engagement across stakeholders. For consideration, recent examples for RWE have been held in the US, leading up to the FDA's guideline development.

- Demonstration projects are essential to increase knowledge, capacity and confidence levels amongst RWD stakeholders including pharmaceutical companies and regulators. Piloted approaches are also ongoing in other countries and regions (3), and EMA should remain active in this field of research internationally. Moreover, enhanced acceptability of RWD to support regulatory decisions must also involve and evolve with patients, HTA bodies, healthcare professionals and other stakeholders. The EMA RSS 2025 also includes an objective to "develop a capacity that will enable the Agency to rapidly and securely access and analyse large amounts of healthcare data". It is recommended that such a capacity (e.g., system or algorithm) should be developed in consultation with relevant stakeholders including industry.
- Build on ongoing efforts (in EU and internationally) to provide clarity on scope and quality of sources of RWE;
- Seek to align and contribute to extend the standards and methodologies for collecting, analysing and validating RWE use internationally; and
- Action on preparing an international guideline of good practice for RWD

1.7. NEW! Deliver secure ethical patient-focussed governance for accessing, managing analysing and assessing real world data

- Collaborate with regulatory authorities, especially Data Protection Agencies, and where appropriate European Data Protection Board (EDPB) to facilitate a harmonised approach regarding the use of RWD/big data, especially the re-use of data for secondary purposes, and diminish barriers that might hamper big data use.
- Seek to align and contribute to extend the standards and methodologies for collecting, analysing and validating RWE use internationally. This should also incorporate the current recommendations under consultation in the Discussion Paper "Use of patient disease registries for regulatory purposes – methodological and operational considerations".
- Governance Better involve patients in adverse event reporting
- Action on preparing an international guideline of good practice for RWD
- Demand better statistical analysis of observational data (incl. public registration of a detailed study protocol and analysis plan, before start of the study)

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

Underlying actions

1.1. Encourage new business models that provide "pull" incentives or different approaches beyond the current "funding research" strategy in the EU, including mechanisms for sustained availability for new and old antibiotics

- In addition to fostering new antibiotics, the EMA should also consider the reinforcement of arrangements which ensure that essential medicines are maintained on the market, in particular for old antibiotics that are being utilised in new ways.
- The strategy so far adopted to support development of new antimicrobials is not leading to the expected results. More than continuing with the current approach, different tools could be explored
- AMR is a dramatic example reflecting the pitfalls of a system which relies too much on the outputs of an industry-based model. Instead of looking again to new business models and new incentives, the international community should support independent public research infrastructures. It is a "variation" on C but needs to be discussed.
- Work with the European Commission and member states to create a framework of procurement incentives for off-patent and generic antibiotics such as multi-winner tenders and non-price selection criteria, to ensure a stable supply of highly-effective antibiotics.
- Optimise the regulatory pathway for older antibiotics that have previously been unavailable in some or all European markets and provide incentives by means of a reduction in regulatory fees for Marketing Authorisation Applications;
- Develop an evidence-based list of critical off-patent antibiotics with a multi-sector stakeholder group?
- Prevent future market exit by providing targeted regulatory relief for MAHs of critical antibiotics. EMA could do this through decreased cost of maintaining authorisations via a reduction in post-approval regulatory fees or an introduction of a special reduced annual fee structure applicable to antibiotics for these vital public health products;

1.2. In collaboration with HTAs and payers, define the evidence requirements for new antibacterial medicines

- The proposal for EMA to work with HTA bodies to define and explain the relevance of evidence requirements for new antibacterial medicines is much needed. We must also recall the importance for development of better diagnostics to improve stewardship and limit diseases.
- Industry also welcome proposals to work with HTA bodies to define and explain the relevance of evidence requirements for new antibacterial medicines. The unique development challenges of antibiotics are poorly understood by many stakeholders, and industry would welcome partnership with EMA to better explain the evidentiary standards and basis for assessment.

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

- Further regulatory support for antibiotic development, which offers the support and potential to expedite assessment along the lines of PRIME, is still needed to bring these needed treatments more quickly online.
- Continue to support development of new antibacterial agents and their alternatives (Rec. 4.2); Industry continue to advocate for collective action to address AMR and we welcomes proposals to support the development of new medicines to combat AMR.
- Existing emerging health threats regulatory procedures should be summarized in a comprehensive way to give guidance and quick answers for developers.

1.4. Support the development and application of rapid diagnostic tools.

- We would like EMA to support the development and application of both PoC diagnostics and self-tests. For example, self-test (at home or in a pharmacy) allowing a patient to detect whether his/her sore throat is due to a virus or a bacteria can allow self-medication (virus) or reference to a doctor (bacteria). This would best serve, patient and the healthcare system as a whole by preventing secondary effect of untreated strep throat in one case or unneeded doctor visit and antibiotic prescribing and thus tackle AMR in the other.

1.5. Support initiatives, such as the clinical trials network, to facilitate and accelerate clinical development

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:

Underlying actions

1.1. Establish a platform for EU benefit-risk monitoring of vaccines post-approval

- The experience with seasonal influenza vaccines illustrates the difficulty to generate post-approval effectiveness data in Europe. The cooperation between regional and national surveillance networks is essential to generate quickly meaningful data on the benefit/risk of prophylactic vaccines. The review of ADVANCE and DRIVE experience may bring important learnings for the creation of a platform to monitor the post-approval benefit/risk of vaccines. Industry should be involved as stakeholder for this topic.
- Establishing a platform for EU benefit-risk monitoring of vaccines post-approval will deliver benefits for all stakeholders, and a review of the IMI's ADVANCE and DRIVE programmes can support that effort.
- The incorporation of RWD surveillance efforts into efforts that would provide increases in approaches in post-authorisation monitoring of vaccinations. Large, multi-national systems, such as VigiBase are fundamentally important. Better RWD platforms, potentially linked to electronic health records, would promote this core recommendation.

1.2. Communicate proactively with key stakeholders on benefit-risk using evidence-based tools to tackle vaccine hesitancy

- It is key that accurate and science-based information on the benefit-risk of vaccine is communicated to the public.
- Vaccine hesitancy is significant health risk for EU citizens, it has been driven by insufficient health literacy levels combined with susceptibility to misleading information. Special attention should be given to developing local networks and communication tools which can be deployed across a range of channels to rebuild trust in vaccines.

1.3. Examine innovative clinical trial approaches to expedite vaccine development

- Consider early PRIME applications of non-SME companies for vaccines based on proof of principle data. The substantial time needed for vaccine clinical studies & development costs makes it challenging for companies to develop vaccines; this would allow for regulator input on vaccine innovative clinical trial design early in the development. This could shorten the timeline to bring vaccines to the people.
- Classical development of vaccines is long and costly. Promoting innovative clinical trial design allowing to demonstrate positive benefit/risk with a reduced number of subjects in phase 3 is key to deliver new vaccines quicker to the patients. For some vaccines (e.g. improved pertussis, Group B Streptococcus) demonstration of efficacy prior to marketing authorisation will not be feasible. Regulatory acceptance of initial approval based on alternative approaches such as surrogate endpoints or human/animal challenge models combined with post-approval real world data is essential. Acceptability by recommending bodies of such approaches is also key to facilitate access to innovative products. Finally, as manufacturers are conducting global developments, cooperation between major regulatory agencies is needed to guarantee global acceptance of these approaches.
- The clinical landscape is changing more quickly than the regulatory framework within the EU; EMA could consider closer engagement with other regulatory bodies such as WHO, national African regulators to adapt its thinking and to influence as needed.
- We believe that the advancement of methods/tools (e.g. biomarkers) to characterise immune response should facilitate the identification of correlates of protection and surrogate markets and support the development of new approaches (e.g. in vitro methods to identify measurable characteristics of safety, quality and potency).
- The potential to promote innovative clinical trial design will allow manufacturers to demonstrate positive benefit/risk with a reduced number of subjects recruited for Phase III trials. Both of these actions will expedite innovative development.
- Promoting innovative clinical trial design

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

- Advance methods/tools to characterise immune response should 1) facilitate the identification of correlates of protection and surrogate markers which will enable the development of innovative vaccines, 2) support the development of new approaches such as in vitro methods to identify measurable characteristics of product safety, quality, and potency.

1.5. Engage with public health authorities and NITAGs to better inform vaccine decisions

- It is important for vaccine developers to be aware of the positions of recommending bodies/payers in the different Member States on the product profiles they would consider of interest for their country/region. In absence of such systematic early and continuous dialogue, vaccine companies pursue their efforts to develop safe and efficacious vaccines, some of which may ultimately never be included in the national/regional immunisation programmes. For example, a vaccine authorised by regulators based on a demonstrated high level of efficacy may not be considered attractive from a public health perspective if it does not contain some antigens (e.g. does not target some serogroups) and thus may not be recommended in certain countries/regions. Another challenge is

that the data generated to support the marketing authorisation of a vaccine are not necessarily the same as the data (usually cost-effectiveness data based on local epidemiology and standards of care) that recommending bodies/payers in the different EU Member States want to have available prior to their decision making. Considerable efforts are being made at the EU level to foster early dialogue with regulators and HTABs through parallel scientific advice procedures. However, for vaccines, NITAGs are responsible for providing independent, evidence-informed advice to health authorities on policy issues related to immunisation and vaccines.

- The roles of NITAGs and HTABs in the decision-making process vary from country to country. Now that parallel CHMP/HTA scientific advices have shown their added value, the possibility to involve NITAGs in parallel CHMP/HTA/NITAG scientific advices for prophylactic vaccines should be explored. A pilot took place in 2018, we encourage EMA to continue working with all stakeholders on this topic.
- Pursue systematic early and continuous open dialogue with EMA, public health authorities and NITAGs to better inform decision-making.

1.6. NEW! Advance understanding of the science behind novel technology so to ensure appropriate regulatory oversight and foster ability to exploit value of platform technologies in view of emerging threats

- Novel manufacturing technologies: novel manufacturing technologies are key enablers for effective and sustainable supply of products. It is crucial to understand the regulatory implications of novel approaches. Gaps in regulatory framework should be identified and strategies established to address them.
- In light of developing technologies e.g. platforms used in vector (including bacteriophage) derived medicines develop guidelines that enable the concept of a "drug master file" type approach to be used across different clinical trial applications for different vaccines using the same vector (e.g. stability data, tox data, safety).

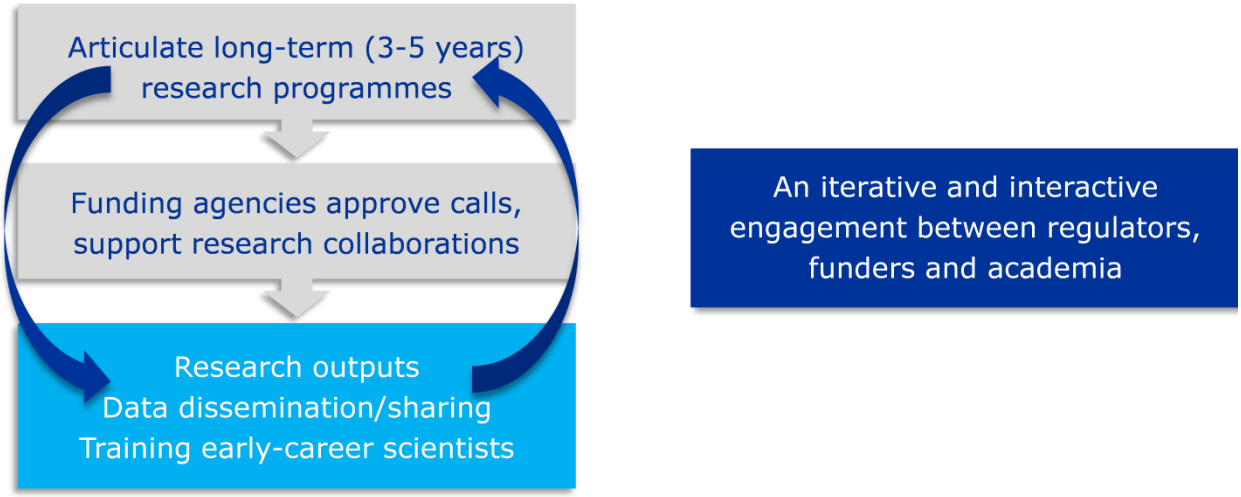
1.7. NEW! Harmonise regulatory framework for conduction of vaccines clinical trials including during emergencies

- The landscape across the EU for emergency use of vaccines is rather heterogeneous. In addition, GMO requirements and requirements for challenge material for human challenge studies vary across MSs. A more conducive and predictable environment for vaccines clinical research is warranted.
- Develop guidelines to allow for harmonized GMO assessment across the EU instead of individual national procedures- these latter can be time-consuming.

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.

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



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:

Underlying actions

1.1. 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)

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

1.2.1. Collaboration with academic research centres

- Collaboration with academic research centres, such as the Future Targeted Healthcare Manufacturing Hub as well as other non-commercial research institutions

- The strategic plan should mention the opportunities that will arise from working with qualified clinical research networks on the development of clinical development programmes and the execution of clinical trials.
- Developing structured approaches for these networks to contribute to the work of the regulatory network (including training, quality control of expert advice, and work towards data sharing) will enhance the EMA's current ad hoc approach to engagement with academics.
- Specifically, it is noted that the output of many IMI projects comprised of tools and methods with potential regulatory impact. IMI has developed guidance for projects to raise awareness of the various opportunities to interact with regulators in the framework of research on regulatory sciences with a potential impact on public health. We encourage EMA to post this guidance on its website. https://www.imi.europa.eu/resources-projects/guidelines-engaging-regulators

1.2.2. Role of industry in this partnership

- It is important to include industry in this endeavour to maximize transparency and cooperation on regulatory science. The regulatory science discussion should be defined, fuelled, and driven by industry's pipeline – not as a siloed academic exercise.
- Dialogue should be encouraged between academia, regulators but also with developers and manufacturers so as to bring together the necessary scientific, regulatory but also practical and industrial considerations.
- In addition to engagement with academics across the EU, we would encourage EMA to also prioritize work with sponsors, data vendors, patients, professional and clinical societies, and other stakeholders and to share learnings broadly. A diversity of opinions can provide valuable input to advance the regulatory science foundation, particularly as it relates to RWE, and ultimately advance patient care.
- Include pharmaceutical industry researchers in the network-led partnerships that direct priority areas for fundamental research based on the regulatory science strategy (e.g., PROs, 'omics, AI, drug-device combinations, M&S).

1.2.3. Training/education

- This proposal could also be extended to include collaboration with students, as it is critical for Europe to have a pipeline of talent to support the long-term future of regulatory science.
- Also, specific educational schemes for regulatory science should be promoted by EMA with educational postgraduate institutions and research institutions to provide educational tools to research communities.
- We are deeply concerned about the lack of experts in regulatory science within research institutions responsible for the development of the European research agenda. In this context, a specific recommendation to tackle this barrier should be introduced in the strategy.
- We need to prioritize Regulatory science specific PhD training networks to train talented graduates on the regulatory tools and skillset required to develop their career further within a regulatory setting. We could also consider joint academic –regulatory graduate supervision models. There are already some good models in Europe e.g. www.pearrl.eu and https://www.regulatoryscience.nl/editions/2019/08/promovendi but we need to role this out EU wide.

- We advocate a graduate training model for PhD graduates to pursue careers in Regulatory settings.
- Academia could also play an important role in defining novel clinical trial designs and developing methods to enable adequate analyses of data obtained.
- PRIME: we want to insist on the need to have appropriate expertise available in the European regulatory network to guarantee access to PRIME to all categories of products, including prophylactic and therapeutic vaccines

1.2.4. Funders

- Development of innovative funding models for translating bioscience research into new therapies, including advanced therapies
- Explaining incentive models to all stakeholders, including from public research and public services (EU and national).
- Provide funding opportunities for collaborative regulatory science initiatives at regional levels within the EU

1.2.5. European/global consortia

- EMA resources could be more effectively leveraged through active participation in global consortia.
- It is proposed to actively develop systematic ties for regulatory science with a common Network strategy between all NCAs and the EMA. Several of the NCAs, including the MEB, have a long-standing experience in conducting regulatory science

1.2.6. Regulatory science priorities

- "Urge EMA to continue to expand its support of public-private partnerships (PPPs) and consortia-based programs...The work achieved through PPPs is made publicly available to maximize the benefits of its work. Stakeholder consensus allows a field to move faster and farther than an individual entity is able to. Precompetitive PPPs also provide a means for regulatory agencies to engage with stakeholders to align the work with regulatory thinking. In this paradigm, scientific research is focused on the regulatory processes of developing new medicines, which is often an afterthought without input from regulators. When successful, the benefits are felt by researchers, drug developers, regulators, and patients, with therapeutic areas that have lacked the interest of developers becoming revitalized. Further, the setbacks of inevitable failures are shared, and thus, the overall impact is minimized. PPPs and consortia allow for the execution of the collaborative efforts found throughout the strategic vision and are the catalyst to innovation across drug development.
- We believe that a specific underlying action should be added to this recommendation, to create with these stakeholders, regulatory science priorities to be incorporated into national and European translational calls, particularly in the field of novel therapies.