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Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle

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Reflection paper on the use of AI in the medicinal product lifecycle

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1. Introduction

The utilisation of artificial intelligence (AI) is an important part of the digital transformation. Such systems are often developed through the process of machine learning (ML) where models are trained from data, with or without human input. However, as these models often contain exceptionally large numbers of trainable parameters arranged in non-transparent model architectures, new risks are introduced that need to be mitigated to ensure the safety of patients and integrity of clinical study results. Also, as the overarching approach is inherently data-driven, active measures must be taken to minimise the integration of bias into AI/ML applications and promote reliable and trustworthy AI.

This reflection paper provides considerations on the use of AI/ML in the lifecycle of medicinal products, including medicinal products development, authorisation, and post-authorisation. Given the rapid development in this field, the aim of this reflection paper is to reflect on the principles that are relevant for regulatory evaluation when these emerging technologies are applied to support safe and effective development, manufacturing and use of medicines.

It is crucial to identify aspects of AI/ML that would fall within the remit of EMA or the National Competent Authorities of the Member States as the level of scrutiny during assessment will depend on this remit. This reflection paper focuses only on the use of AI in the medicinal product lifecycle and any references to qualification of novel methodologies for medicines development[1] and regulatory interaction are to be understood within this scope. Additionally, medical devices with AI/ML technology can be used within the context of clinical trials to generate evidence in support of a marketing authorisation application and/or can be combined with the use of a medicinal product. In such cases EMA will be involved in the assessment on whether the device is adequate to generate evidence, supporting an EU marketing authorisation. Similarly, if a device is used to provide recommendations in the Summary of Product Characteristics, e.g., on posology or monitoring, the EMA will assess all relevant aspects of the proposed combined use.

This reflection paper describes the current experience of EMA in a field where scientific knowledge is fast evolving. It should be read in coherence with both legal requirements and overarching EU principles and legislation on AI (including the AI act and AI liability directive), data protection (including GDPR), cyber security (including the Cybersecurity act), and medicines regulation (see references).

While some considerations in this reflection paper are of general interest for the development of veterinary medicinal products, important differences exist between the human and veterinary domain including legal bases, regulatory requirements and guidance, ethical issues, risks of bias and other sources of discrimination. Further reflections will be necessary to better identify the specific circumstances and sources of bias in the veterinary setting. While veterinary medicines regulated by Regulation (EU) 2019/6 are generally within the scientific scope of this document, the reader is advised to pay attention to notes pointing out fundamental differences. Specific veterinary reflections or guidance may be developed in the future.

2. Discussion

2.1. Definitions and scope

According to the OECD definition, an AI system is a machine-based system designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment and that, for explicit

[1] Qualification of innovative development methods is applicable to human medicines provided by EMA CHMP (see Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu))

or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environment.

In this reflection paper the term AI/ML is used to cover all models developed through the process of ML, regardless of the specific model architecture.

2.2. General considerations

AI/ML tools and methodologies can, if developed and used correctly, effectively support the acquisition, transformation, analysis, and interpretation of data within the medicinal product lifecycle. It should be noted that many recommendations, best practices, and previous learnings within areas of model-informed drug development and biostatistics also apply to the field of AI/ML. Related methodology guidelines which may be relevant are listed in at the end of this document.

A risk-based approach for development, deployment, and performance monitoring of AI/ML tools allows developers to pro-actively define the risks to be managed throughout the system lifecycle. This paper uses the term "high patient risk" for systems affecting patient safety, while the term "high regulatory impact" is used for cases where impact on regulatory decision-making is substantial.

Advice on risk management will be further reflected in future regulatory guidance, since the impact of system malfunction or suboptimal model performance can range from minimal to critical or even life-threatening. The degree of risk depends not only on the AI technology and data quality, but also on the context of use and the degree of influence the AI technology exerts. In addition, the degree of risk may vary throughout the lifecycle of the AI-system. Clinical trial sponsors, marketing authorisation applicants, marketing authorisation holders (MAHs) and manufacturers planning to deploy AI/ML technology are expected to consider and systematically manage relevant risks from early development to decommissioning.

If an AI/ML system is planned for use in the context of medicinal product development, evaluation, or monitoring, and is expected to impact, even potentially, on the benefit-risk balance of a medicinal product, early regulatory interaction is advised (see Regulatory interactions). 1The level of scrutiny depends on the level of risk and regulatory impact posed by the system.

A key principle is that it is the responsibility of the clinical trial sponsor, marketing authorisation applicant/holder or manufacturer to ensure that all algorithms, models, datasets, and data processing pipelines used are fit for purpose and are in line with legal, ethical, technical, scientific, and regulatory standards as described in EU legislation, GxP standards and current EMA guidelines. Of note, these requirements may in some respects be stricter than what is considered standard practice in the field of data science.

For all requests for advice or opinions the applicant or MAH is expected to provide a scientific base along with sufficient technical details to allow comprehensive assessment of AI systems used in the medicinal product lifecycle, including the integrity of data used for model development and the generalisability of model performance to the target population and the specific context of use.

2.3. AI in the lifecycle of medicinal products

The following sections are structured along the lifecycle of medicinal products, from drug discovery and development to post-authorisation settings such as pharmacovigilance and effectiveness studies.

2.3.1. Drug discovery

The application of AI/ML in the process of drug discovery can be low regulatory impact if non-optimal performance only affects the developer. However, if results contribute to the total body of evidence presented for regulatory review, principles for non-clinical development (see below) should be followed. In this context, all models and datasets used should be reviewed by the sponsor to mitigate ethical issues, risks of bias and other sources of discrimination against non-majority genotypes and phenotypes from a data quality and quantity perspective (see Technical aspects – Data acquisition and augmentation).

2.3.2. Non-clinical development

AI/ML applications in non-clinical development may strive not only to achieve improved performance in data analysis and interpretation but could potentially also include AI/ML modelling approaches to replace, reduce, and refine the use of animals and improve human translatability. Existing Standard Operating Procedures (SOPs) would be expected to extend to all AI/ML applications in non-clinical studies. When the *OECD Series on Principles of Good Laboratory Practice (GLP)* is applicable, advisory documents on Application of *GLP Principles to Computerised Systems (no.17)* and *GLP Data Integrity (no. 22)* should be considered.

While non-clinical development may allow an iterative data-driven AI/ML approach, prospective model performance testing during development and pre-specified analyses during inference may be needed for specific cases. Applications that affect patient safety (such as efficacy and safety modelling that inform the design of "first-in-human" studies), that are potentially relevant for assessment of the benefit-risk balance of a medicinal product, or have high regulatory impact in another manner, should be developed and tested accordingly.

2.3.3. Clinical trials

2.3.3.1. Good clinical practice (GCP)

The use of AI/ML within the context of clinical trials should meet applicable requirements in the *ICH E6 guideline for good clinical practice (GCP)* or *VICH GL9 Good clinical practices (veterinary)*. Of note, if the use could be of high regulatory impact or high patient risk in a clinical trial, and the method has not been previously qualified by the EMA for the specific context of use, the full model architecture, logs from model development, validation and testing, training data and description of the data processing pipeline would likely be considered parts of the clinical trial data or trial protocol dossier and thus may be requested for comprehensive assessment at the time of market authorisation, clinical trial application or GCP inspection.

Additional information would need to be considered when applying AI/ML in a clinical trial setting where the impact on specific aspects such as the design and conduct of the trial, the use of decentralised elements and the intended use as a decision support software should be reflected in the specific protocol benefit-risk assessment.

2.3.3.2. Use of medical devices and in vitro diagnostics in clinical trials

Medical devices and *in vitro* diagnostics (IVDs) are regulated according to the Regulation (EU) 2017/745 on Medical Devices (MDR) or Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR). Applications within areas of medicines development and use can include an interplay with such devices. Hence, this section is provided for completeness and without prejudice to the existing guidance on medicinal products used in combination with medical devices.

When AI/ML systems are used for clinical management of an individual patient, they may be considered medical devices according to MDR or IVDR[2,3]. Specific guidance on the Qualification and Classification of Software within the framework of the MDR and IVDR can be found in MDCG 2019-11[3]. It is not in the remit of the EMA to qualify or classify software under the above regulations.

Even when using CE marked medical devices, fulfilment of additional requirements may be needed to qualify it for use within the context of a clinical trial, to ensure the rights, safety, wellbeing of subjects, integrity of data and results of the clinical trial including their generalisability.

2.3.3.3. Data analysis and inference

When AI/ML models are used for transformation, analysis or interpretation of data within a clinical trial of a medicinal product, they are considered a part of the statistical analysis and should follow applicable guidelines on statistical principles for clinical trials (see Related methodology guidance) and include analysis of the impact on downstream statistical inference. For inference in late-stage clinical development, this requires a detailed description of a pre-specified data curation pipeline and a frozen and documented (see Technical aspects) or EMA qualified (see Regulatory interactions) set of models, within the statistical analysis plan.

Early-phase clinical trials

Use of AI/ML models for data analysis in early stages of clinical development is often low risk, but can contain applications with high patient risk such as treatment assignment or dosing. In all cases, measures should be taken to ensure that all estimates used for planning of subsequent clinical trials are statistically robust and that exploratory analyses are interpreted in relation to multiplicity. In circumstances where data from early-phase clinical trials may have a substantial regulatory impact, such as in limited clinical development programs, requirements may be higher and should be discussed through early regulatory interaction.

Pivotal clinical trials

In late-stage pivotal clinical trials, all risks related to overfitting and data leakage must be carefully mitigated. Prior to model deployment in high regulatory impact settings, such as in relation to the primary endpoint, performance should be tested with prospectively generated data (future calendar time) that is acquired in a setting or population representative of the intended context of use. Incremental learning approaches are not accepted, and any modification of the model during the trial requires a regulatory interaction to amend the statistical analysis plan.

Prior to the database lock and subsequent unblinding of the data used for hypothesis testing, the data pre-processing pipeline and all models should be frozen and documented in a traceable manner in the statistical analysis plan. Once a dataset has been opened, any non-prespecified modifications to data processing or models implies that analysis results are considered *post hoc* and hence not suited for confirmatory evidence generation.

If possible, it is encouraged that models are published in an openly accessible repository prior to their deployment in a pivotal clinical trial, to allow third-party review and promote standardisation.

[2] Regulation (EU) 2017/745 and Regulation (EU) 2017/746 apply to human medicines only.

[3] See MDCG 2019-11 guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 (MDR) and Regulation (EU) 2017/746 (IVDR) (link) and infographic on classification of software as medical device (link)

2.3.4. Precision medicine[4]

AI/ML can be used to individualise treatment in relation to factors such as disease characteristics, patient genotype, wide-band biomarker panels and clinical parameters. This could include patient selection, dosing, *de novo* design of product variants and selection from a pre-manufactured library of variants. It is possible that an AI/ML application is referenced in the Summary of product characteristics to aid such decisions on indication and posology. Without prejudice to the need for conformity assessment by other regulatory bodies, the safety and efficacy of the medicinal product together with the AI-driven application is a matter for medicines regulation.

Applications of AI/ML in relation to indication or posology are regarded as a high patient risk as well as high regulatory impact. In addition to the principles spelled out elsewhere in this document for such settings, special care should be paid in defining what constitutes a change in indication or posology which would requiring a regulatory evaluation before implementation. Also, it is important to provide guidance that the prescribers can critically apprehend and to include fall-back treatment strategies in cases of technical failure.

2.3.5. Product information

AI/ML applications used for drafting, compiling, editing, translating, tailoring, or reviewing medicinal product information documents should be used under close human supervision. Given that generative language models are prone to include plausible but erroneous or incomplete output, quality review mechanisms need to be in place to ensure that all model-generated text is both factually and syntactically correct before submission for regulatory review.

2.3.6. Manufacturing

The use of AI/ML in the manufacturing of medicinal products including process design and scale up, process optimisation, in-process quality control and batch release is expected to increase in the coming years. Model development, performance assessment and life-cycle management should follow the quality risk management principles, taking patient safety, data integrity and product quality into account. For human medicines the principles of ICH Q8, Q9 and Q10 should be considered, awaiting revision of current regulatory requirements and GMP standards.

2.3.7. Post-authorisation phase

It is foreseen that AI/ML tools can effectively support post-authorisation activities, such as post-authorisation efficacy and safety studies (PAES and PASS) for human medicines and post-marketing surveillance studies for veterinary medicines, as well as pharmacovigilance activities including adverse event report management and signal detection, in line with current good pharmacovigilance practices requirements available for both human and veterinary medicines.

Applications within pharmacovigilance may allow a more flexible approach to AI/ML modelling and deployment, where incremental learning can continuously enhance models for classification and severity scoring of adverse event reports as well as signal detection. However, it remains the responsibility of the MAH to validate, monitor and document model performance and include AI/ML operations in the pharmacovigilance system, to mitigate risks related to all algorithms and models used.

[4] Precision medicines in this context applies to human medicines only.

If a post authorisation study is listed as a condition for a marketing authorisation, AI/ML applications should be discussed within a regulatory procedure unless details are agreed already at time of authorisation. Of note, the same requirements of using a pre-specified statistical analysis plan, data pipeline and frozen models as for pivotal clinical trials, may apply.

2.4. Regulatory interactions

Applicants and developers are expected to perform a regulatory impact and risk analysis of all AI/ML applications and are recommended to seek regulatory interactions when no clearly applicable written guidance is available. The regulatory impact is directly related to the phase in the medicinal product lifecycle and the weight of evidence these data will have in the intended setting. In cases where impact on regulatory decision-making may be high, interaction with regulators is always recommended.

Early interaction on experimental technology is provided by the EMA Innovation Task Force (ITF). Scientific advice and qualification[1] of novel methodologies in medicines development is provided by the Scientific Advice Working Party (SAWP) of the CHMP and the Scientific Advice Working Party (SAWP) of the CVMP. The term qualification advice/opinion refers to novel methodologies applied to medicinal product development where the methodology to be qualified would ideally be medical device/software agnostic.

Timing of interactions should be guided by the regulatory impact and risk associated with using the AI based models in context of the lifecycle of a medicinal product. In high-impact cases, interaction may be crucial already at the planning stage.

The documentation to inform the interaction with regulators should cover questions such as intended context of use, generalisability, performance, robustness, transparency, and clinical applicability, at a level of detail sufficient for comprehensive assessment. Specific and clearly formulated regulatory and scientific questions are strongly encouraged, to allow reciprocally concise answers.

2.5. Technical aspects

2.5.1. Data acquisition and augmentation

AI/ML models are intrinsically data-driven, as they extract or adapt their parameters from training data. This makes them vulnerable to the integration of bias into models. Efforts should be made to acquire a balanced and sufficiently large training dataset in relation to the intended context of use. The need to over-sample rare populations should be considered, taking all relevant bases of discrimination as specified in the EU principle of non-discrimination and the EU fundamental rights into account. Dedicated reflections will be necessary to identify data quality issues and potential biases applicable to veterinary medicines considering the difference e.g., in target populations and regulatory requirements between veterinary and human medicines.

The source(s) of data and the process of data acquisition, along with any processing such as cleaning, transformation, imputation, annotation, normalisation, and augmentation should be documented in a detailed and fully traceable manner in line with GxP requirements.

Exploratory data analyses should be performed to describe the data characteristics, representativeness, fairness, and relevance for the intended task. At a minimum, there should be documented considerations on:

- relevance and population representativeness of data, and intra-/extrapolation assumptions made,

- class imbalances and corresponding mitigation measures taken, and
- potential risk for unfair or discriminatory outcomes from using the data.

Augmentation techniques may be applied to expand the training dataset. For imaging data this includes, but is not limited to, geometric transformations, truncation and merging, addition of noise and of change of contrast/brightness/colour depth/resolution of imaging data. Similarly, synthetic data of other modalities may in some cases be useful for expanding the training dataset, both for increasing model performance and in relation to non-discrimination.

If limitations in the training dataset remain, affecting the generalisability or fairness of the model, these should be clearly presented in the model documentation along with recommendations on the use of alternative methods in cases for which the model is not considered applicable.

2.5.2. Training, validation, and test datasets

The term validation is often used differently between the fields of AI/ML and medicines development. For AI/ML, validation refers to the data used to inform on the selection of model architecture and hyperparameter tuning and is hence part of the data driven process. The validation subset can be static or iteratively sampled from the training data using cross-validation. Once this process is completed, the final performance of the model is evaluated once using the hold-out test data set. If test performance is unsatisfactory and further model development is needed, the current test data set cannot be re-used for this purpose and a completely new and independent test dataset is required to repeat the test procedure for an updated model.

The practice of an early train-test split into separate and unrelated datasets, prior to any normalisation or other types of processing where aggregated measures are used, is strongly encouraged. Even so, the risk of direct or indirect (often unintentional or even unconscious) data leakage cannot be completely excluded. For example, unknown case overlaps in clinical databases, sponsor-specific basic features shared between study protocols or even general *a priori* knowledge of global study outcomes can contain information that increases risk of overfitting the model. Hence, models intended for high patient risk and/or high regulatory impact settings (in particular, non-transparent models intended for use in late-stage clinical development) should be prospectively tested using newly acquired data, representative for the future context of use.

2.5.3. Model development

Given the plethora of modelling approaches and architectures, only generally applicable considerations are provided on model development. It is the responsibility of the sponsor, applicant or MAH to ensure that SOPs promote a development practice that favours model generalisability and robustness - particularly for settings where models cannot be updated during deployment - and to keep traceable documentation and development logs to allow secondary assessment of development practices. If a third-party AI model or service is to be used within the medicinal product lifecycle with high regulatory impact or high patient risk, it is expected that the manufacturer of the system has provided such details through a methodology qualification process (see Regulatory interactions) covering the specific context of use.

It is strongly encouraged that methods promoting generalisability are explored and implemented, including regularisation techniques, drop-out, and sensitivity analyses with stratification of training data based on calendar time.

It is of particular importance to avoid overfitting, as this negatively affects generalisability of model performance into future context of use. Overfitting that is the result of non-optimal modelling practises

is usually discoverable in the model test phase. A more problematic cause of overfitting is data leakage from the test dataset into the training/validation environment (see Training, validation and test datasets).

It is important to clearly define the intended use of the model, to allow a validity assessment of development decisions and feature engineering, if applicable.

2.5.4. Performance assessment

The choice of metrics for performance assessment is crucial for an adequate assessment of the model. Preferably, the set of metrics should contain parameters that are insensitive to class imbalances. For classification, this could include the Matthews Correlation Coefficient which considers the full confusion matrix. To identify random effects related to the train-test split, the distribution of performance metrics generated through cross-validation should be presented.

Sensitivity analysis for minority classes and in relation to calendar time is expected, to support the generalisability to data with different class proportions and robustness in relation to uncontrolled secular trends in data at deployment. Pre-defined thresholds for performance metrics that can be related to the context of use and considerations on performance requirements depending on level of patient risk and regulatory impact further support the credibility of model performance.

2.5.5. Interpretability and explainability

To strengthen procedural fairness, accountability and prevention of bias, the use of transparent models is preferred. However, it is acknowledged that several of the most high-performing modelling architectures allow only limited insight into the data representation and abstraction in the model. The use of such *black box* models may be acceptable in cases where developers substantiate that transparent (i.e., interpretable) models show unsatisfactory performance or robustness. Model use should be supported by an underlying general rationale and detailed information on model architecture, hyperparameter tuning, training metrics, as well as validation and test results, along with a pre-defined monitoring and system risk management plan for mitigating non-transparency issues. It is recommended that such applications are discussed in detail within the scope of an EMA qualification[1] or scientific advice procedure.

To allow review and monitoring of black box models, methods within the field of explainable AI should be used whenever possible. This includes providing explainability metrics, such as *SHAP* and/or *LIME* analyses, both for the model and for individual inferences during deployment. Computer vision models, and extensions into other modalities where attention mechanisms are used, should whenever possible be supported by class activation, saliency or attention maps to verify that features are extracted from relevant positions in the image or sequence.

2.5.6. Model deployment

Deployment of AI/ML models should be performed in line with the risk-based approach described for model development. For high patient risk and high regulatory impact use cases, all non-trivial changes in the software and hardware stack supporting the model, including changes for key dependencies, require a re-evaluation of system performance. It is also of importance that the data acquisition hardware, software, and data transformation pipeline at inference is in line with pre-defined specifications.

Monitoring of model performance should be instituted to allow early detection of drift/degradation and thresholds for acceptable model performance should be clearly defined. This may include routine

sampling of data for manual classification or use of externally provided test data sets from external quality control programs. Also, compliance with applicable standards should be regularly evaluated.

For all models, especially those where there is no human-in-the-loop, a system risk management plan should be developed that defines likely risks of failure modes of the algorithm. This includes consequences of incorrect predictions/classifications as well as monitoring and mitigation/correction approaches, such as how to trigger a suspension/decommission of the model and how to suspend or decommission it.

2.6. Governance

SOPs implementing GxP principles on data and algorithm governance should be extended to include all data, models and algorithms used for AI/ML in cases of high regulatory impact or high patient risk. Aspects related to the governance of all components used, the application of data protection and compliance with applicable data protection laws and ethical standards should be documented and regularly reviewed.

2.7. Integrity aspects and data protection

New and not yet fully characterised risks emerge when data is transformed into high-parameter model representations, as these can contain a similar level of subject-level information granularity as the training data but with limited insight into the data representation. For example, if personal data have been used for model training, it must be further evaluated whether such information can realistically be extracted through membership-, inference- and model inversion attacks, to mitigate the risk of re-identification where needed.

Large language models, often containing billions of parameters, are at particular risk of memorisation due to their size. Overfitting increases the risk of memorisation. Regularisation, drop-out and addition of random noise can provide partial to complete anonymisation, depending on the implementation.

In conclusion, if the training data are not fit for sharing, integrity preserving measures to anonymise personal data should be taken prior to transferring a model to a less secure environment.

It is the responsibility of the applicant or MAH to ensure that all personal data, including those indirectly held within AI/ML models, are stored and processed in accordance with Union data protection legislation. Accordingly, all data processing activities must comply with the principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality, accountability as well as the rights of data subjects as well as data protection by design and default.

In the EU, supervision and monitoring of data protection compliance of AI systems falls under the competence of relevant Member State data protection authorities. As a general recommendation in the case of any personal data processing by AI, a specific risk assessment focusing on the AI system should be performed. This should address and document the possible impact on data subject's rights, freedoms and safety, and demonstrate compliance with the above listed principles, including necessity and proportionality of the envisaged use of personal data.

The necessity assessment should reflect on the possibility to use data that does not allow for the (re)identification of a natural person, such as anonymised data. Otherwise, it should be justified why these options are not feasible in view of the objectives pursued.

The proportionality assessment should address the adequacy of the amount and type of personal data to be processed (in line with data minimisation principle) and identify the least intrusive methods of data use to minimise the impact on data subjects.

2.8. Ethical aspects and trustworthy AI

As reflected in the respective sections above, the basic ethical principles for AI listed below apply to all phases of the medicinal product lifecycle for human medicines and, to an appropriate degree for veterinary medicines. These principles were defined in the guidelines for trustworthy AI and presented in the Assessment List for Trustworthy Artificial Intelligence for self-assessment (ALTAI) presented by the independent High-Level Expert Group on AI that was established by the European Commission.

- Human agency and oversight
- Technical robustness and safety
- Privacy and data governance
- Transparency
- Accountability
- Societal and environmental well-being
- Diversity, non-discrimination, and fairness

ALTAI may guide the involved entities, including the developers and deployers of AI in implementing such principles in practice.

To build trust in the effectiveness, reliability, and fairness of AI/ML tools, a human-centric approach should guide all development and deployment of AI and ML. This requires not only that active measures are taken during data collection and modelling (See Technical aspects) but also that both user and patient reported outcome and experience measures are included in the evaluation of AI/ML tools when they interface with an individual user or patient[5].

A systematic impact analysis should be conducted in the early stages of planning and development of AI/ML tools, and expertise on ethical and legal aspects (including data protection to ensure privacy by design) should be onboarded early in all projects. Likewise, impact of use of existing AI/ML tools needs to be assessed at the planning stage of the respective drug development phase to adequately include relevant measures and oversight by design. In this regard, applicants and MAHs are recommended to consider the Ethics guidelines for trustworthy AI by the High-Level Expert Group on AI, set up by the European Commission.

3. Conclusion

In conclusion, the quickly developing field of AI/ML shows great promise for enhancing all phases of the medicinal product lifecycle. In several aspects such as data management, governance, and statistical stringency, currently established regulatory principles, guidelines, and best practices are directly applicable to AI/ML and efforts should be made in all organisations to reciprocally integrate data science competence with the respective fields within medicines development, manufacturing and pharmacovigilance.

[5] For veterinary medicines, it should be further reflected if these principles may translate into user, owner or consumer experiences in the context of treatment of animals.

However, the use of AI models with exceptionally large numbers of trainable parameters arranged in non-transparent architectures introduces new risks that need to be mitigated both during model development and deployment to ensure the safety of patients and integrity of clinical study results. Also, as the overarching approach is inherently data-driven, active measures must be taken to avoid the integration of bias into AI/ML applications and promote AI trustworthiness.

Finally, the use of AI/ML in the medicinal product lifecycle should always occur in compliance with the existing legal requirements, by considering ethics and its underlying principles and with due respect of fundamental rights. A human-centric approach should guide all development and deployment of AI and ML.

4. Glossary

Definitions should be aligned with the definitions contained in the Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts once this regulation has been finally enacted.

AI (artificial intelligence)	Artificial intelligence. OECD definition - an AI system is a machine-based system designed to operate with varying levels of autonomy and that may exhibit adaptiveness after deployment and that, for explicit or implicit objectives, infers, from the input it receives, how to generate outputs such as predictions, content, recommendations, or decisions that can influence physical or virtual environments.
Class imbalance	Imbalances between categories in classification tasks. This affects model performance metrics, e.g., by the fact that a model always predicting the same outcome will be 99% accurate if 99% of test cases belong to the corresponding class.
Data leakage	Direct or indirect propagation of information from the intended test dataset to the model development environment.
Deep learning	Approach to creating rich hierarchical representations through the training of neural networks with many hidden layers
Explainability	The property of systems to provide, often indirect, forms of explanation for their actions.
Feature	A pattern in data that can be reduced to a simpler higher-level representation
Frozen model	A model where all parameters have been finally set, not allowing further adaption to new data.
High patient risk setting	Use cases where errors have consequences for the safety of humans or animals.
High regulatory impact setting	Use cases with substantial regulatory consequences, e.g., affecting the primary endpoint in a late-stage clinical trial.
IVDR	In Vitro Diagnostic Regulation (EU 2017/746)
Interpretability	The property to trace the system's exact behaviour and output in a way that is understandable to a human user.
LIME	Local Interpretable Model-Agnostic Explanations; a technique that approximates any black box machine learning model with a local, interpretable model to explain each individual prediction.
MDR	Medical Device Regulation (EU 2017/745)
ML (machine learning)	Machine learning refers to the computational process of optimising the parameters of a model from data, which is a mathematical construct generating an output based on input data. Machine learning approaches include, for instance, supervised, unsupervised and reinforcement learning, using a variety of methods including deep learning with neural networks.
Model	Mathematical algorithms with parameters (weights) arranged in an architecture that allows learning of patterns (features) from training data
Neural network	Network of one or more layers of neurons connected by weighted links with adjustable weights, which takes input data and produces an output
Overfitting	Learning details from training data that cannot be generalised to new data

Representative	Characteristic of a sample in relation to a reference distribution to possess similar characteristics
SHAP	Shapley Additive Explanations; an explainable AI (XAI) framework that can provide model-agnostic local explainability for tabular, image, and text datasets
Test dataset	Data used to evaluate the performance of the AI system, before its deployment. It is expected to be similar to production data, and proper evaluation needs test data to be disjoint from any data used during development.
Training dataset	Data used specifically in the context of machine learning: it serves as the raw material from which the machine learning algorithm extracts its model to address the given task
Transformation	Change between different representations of data
Transparency	The possibility to fully trace information flow within a model
Validation dataset	Data used by the developer to make or validate some algorithmic choices (hyperparameter search, rule design, etc.).

5. Related methodology guidance

5.1. Guidance concerning human medicines

The following guidelines and other documents may provide useful recommendations for implementing AI/ML applications in the product lifecycle of human medicines:

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH):
    - 'Draft ICH guideline E11A on pediatric extrapolation Step 2b' (EMA/CHMP/ICH/205218/2022) (6 April 2022) <draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf (europa.eu)> (Accessed 26 May 2023)
    - 'ICH E9 Statistical Principles for Clinical Trials' (EMA/CPMP/ICH/363/96) (1 September 1998) <E 9 Statistical Principles for Clinical Trials (europa.eu)> (Accessed 26 May 2023)
    - 'ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials' (EMA/CHMP/ICH/436221/2017) (17 February 2020) < E9 (R1) Step 5 addendum on estimands and Sensitivity Analysis in Clinical Trials to the guideline on statistical principles for clinical trials (europa.eu)> (Accessed 26 May 2023)
    - 'ICH E10 Choice of control group in Clinical Trials' (EMA/CPMP/ICH/364/96) (1 January 2001) <E 10 Choice of Control Group in Clinical Trials (europa.eu)> (Accessed 26 May 2023)
    - 'ICH Q8 (R2) on pharmaceutical development' (EMA/CHMP/ICH/167068/2004) (22 June 2017) < Q8 (R2) Step 5 Pharmaceutical Development (europa.eu)> (Accessed 26 May 2023)
    - 'ICH Q9 (R1) on quality risk management' (EMA/CHMP/ICH/24235/2006) (26 July 2023) <ICH guideline Q9 (R1) on quality risk management (europa.eu)> (Accessed 29 May 2024)
    - 'ICH Q10 (R1) on pharmaceutical quality system' (EMA/CHMP/ICH/214732/2007) (1 June 2008) <ICH guideline Q10 on pharmaceutical quality system - Step 5 (europa.eu)> (Accessed 29 May 2024)

- European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (formerly The European Agency for the Evaluation of Medicinal Products Committee For Proprietary Medicinal Products (CPMP)):
    - 'Draft guideline on multiplicity issues in clinical trials' (EMA/CHMP/44762/2017) (15 December 2016) <Guideline on multiplicity issues in clinical trials - for publication (europa.eu)> (Accessed 26 May 2023)
    - 'Guideline on adjustment for baseline covariates in clinical trials' (EMA/CHMP/295050/2013) (26 February 2015)' <Guideline on adjustment for baseline covariates in clinical trials (europa.eu)> (Accessed 26 May 2023)
    - 'Guideline on missing data in confirmatory clinical trials' (EMA/CPMP/EWP/1776/99 Rev. 1) (24 June 2010) <guideline-missing-data-confirmatory-clinical-trials_en.pdf (europa.eu)> (Accessed 26 May 2023)
    - 'Guideline on computerised systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023) (9 March 2023)' <Guideline on computerised systems and electronic data in clinical trials (europa.eu)> (Accessed 15 July 2024)
    - 'Guideline on registry-based studies' (EMA/426390/2021) (16 September 2021) <Guideline on registry-based studies (europa.eu)> (Accessed 26 May 2023)
    - 'Guideline on reporting the results of population pharmacokinetic analyses' (CHMP/EWP/185990/06) (21 June 2007) <Guideline on Pop PK reports - Adopted (europa.eu)> (Accessed 26 May 2023)
    - 'Guideline on the investigation of subgroups in confirmatory clinical trials' (EMA/CHMP/539146/2013) (31 January 2019) <Guideline on the investigation of subgroups in confirmatory clinical trials (europa.eu)> (Accessed 26 May 2023)
    - 'Points to consider on application with 1. Meta-analyses; 2. One pivotal study' (EMA/CHMP/EWP/2330/99) (31 May 2001) <Points to consider on application with 1. meta-analyses; 2. one pivotal study (europa.eu)> (Accessed 26 May 2023)
    - 'Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design' (EMA/CHMP/EWP/2459/02) (18 October 2007) <Reflection Paper on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive Design (europa.eu)> (Accessed 26 May 2023)
- Medical Device Coordination Group
    - 'MDCG 2022 – 5 - Guidance on borderline between medical devices and medicinal products under Regulation (EU) 2017/745 on medical devices' (April 2022) <mdcg_2022-5_en.pdf (europa.eu)> (Accessed 15 July 2024)

5.2. Guidance concerning veterinary medicines

The following guidelines and other documents may provide useful recommendations for implementing AI/ML applications in the product lifecycle of veterinary medicines:

- The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH):
    - 'VICH GL9 on good clinical practices' (CVMP/VICH/595/98-FINAL) (4 July 2000) <VICH Topic GL9 (GCP) (europa.eu)> (Accessed 20 June 2023)

- European Medicines Agency Committee for Veterinary Medicinal Products (CVMP):
    - 'Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010-Rev.1) (15 July 2021) <GL on statistical principles for clinical trials for VMPs (pharmaceuticals) (europa.eu)> (Accessed 20 June 2023)
    - 'Guideline on clinical trials with immunological veterinary medicinal products' (EMA/CVMP/IWP/260956/2021) (19 January 2021) <Guideline on clinical trials with immunological veterinary medicinal products (europa.eu)> (Accessed 20 June 2023)

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2. European Commission, 'Infographic - Is your software a Medical Device?' (23 March 2021) < Infographic - Is your software a Medical Device? (europa.eu)> (Accessed 21 June 2023)[6]
3. European Commission, Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts, COM/2021/206 final [2021] Available at: EUR-Lex - 52021PC0206 - EN - EUR-Lex (europa.eu) (Accessed 24 May 2023)
4. European Commission, Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006, COM/2023/193 final [2023]. Available at: EUR-Lex - 52023PC0193 - EN - EUR-Lex (europa.eu) (Accessed 24 May 2023)[7]
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6. EU regulatory framework on AI <https://digital-strategy.ec.europa.eu/en/policies/regulatory-framework-ai> (Accessed 15 July 2024)
7. European Commission High-Level Expert Group on AI <https://digital-strategy.ec.europa.eu/en/policies/expert-group-ai> (Accessed 24 May 2023)
8. European Commission High-Level Expert Group on AI, 'Assessment List for Trustworthy Artificial Intelligence (ALTAI) for self-assessment' (17 July 2020). <https://digital-

[6] Veterinary medicines not in scope.
[7] Partly applicable to human medicines only.
[8] Applicable to human medicines only.

strategy.ec.europa.eu/en/library/assessment-list-trustworthy-artificial-intelligence-altai-self-assessment> (Accessed 24 May 2023)

9. European Commission High-Level Expert Group on AI, 'Ethics guidelines for trustworthy AI' (8 April 2019) < https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai> (Accessed 19 June 2023)

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11. European Medicines Agency Qualification of novel methodologies for medicine development < Qualification of novel methodologies for medicine development | European Medicines Agency (europa.eu)> (Accessed 15 June 2023)[8]

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[9] Applicable to veterinary medicines only.