EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 July 2023
EMA/CHMP/CVMP/83833/2023
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Draft

Draft agreed by Committee for Medicinal Products for Human Use (CHMP) Methodology Working Party	July 2023
Draft adopted by CVMP for release for consultation	13 July 2023
Draft adopted by CHMP for release for consultation	10 July 2023
Start of public consultation	19 July 2023
End of consultation (*deadline for comments*)	31 December 2023

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

Keywords	*Artificial intelligence, AI, machine learning, ML, regulatory, medicine, human medicinal product, veterinary medicinal product*

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

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1. Introduction

Data are generated and used increasingly across sectors, including those related to the lifecycle of medicines. In the healthcare sector, data are captured in electronic format on a routine basis. The utilisation of artificial intelligence (AI) - systems displaying intelligent behaviour by analysing data and taking actions with some degree of autonomy to achieve specific goals - is an important part of the digital transformation that enables increased use of data for analysis and decision-making. Such systems are often developed through the process of machine learning (ML) where models are trained from data without explicit programming. However, as these technologies often use exceptionally great 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 avoid the integration of bias into AI/ML applications and promote AI trustworthiness.

This reflection paper provides considerations on the use of AI and 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 scientific principles that are relevant for regulatory evaluation when these emerging technologies are applied to support safe and effective development 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 into data 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], interaction etc. are to be understood within this scope. However, 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 characteristics of the device is adequate to generate evidence, supporting a 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 on AI, data protection, 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.

[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))

2. Discussion

2.1. General considerations

AI and ML tools can, if 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. Adjacent methodology guidelines which may be relevant are listed in section 5 of this document.

A risk-based approach for development, deployment and performance monitoring of AI and ML tools allows developers to pro-actively defining the risks to be managed throughout the AI and ML tool lifecycle. The concept of risk includes, but is not limited to, regulatory impact.

Advice on risk management will be further reflected in future regulatory guidance, as the impact of system malfunction or degradation of model performance can range from minimal to critical or even life-threatening. The degree of risk may depend not only on the AI technology, 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. Marketing authorisation applicants or marketing authorisation holders (MAHs) 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 used in the context of medicinal product development, evaluation, or monitoring, and is expected to impact, even potentially, on the benefit-risk of a medicinal product early regulatory interaction such as qualification of innovative development methods for a specific intended use in the context of research and development in relation to pharmaceuticals[1] or scientific advice is advised. The level of scrutiny would depend on the level of risk and regulatory impact posed by the system.

A key principle is that it is the responsibility of the marketing authorisation applicant or MAH to ensure that all algorithms, models, datasets, and data processing pipelines used are fit for purpose and are in line with ethical, technical, scientific, and regulatory standards as described in GxP standards and current EMA scientific 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 any AI/ML systems used in the medicinal product lifecycle, the integrity of data and generalizability of models to the target population and for a specific context of use.

2.2. 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.

2.2.1. Drug discovery

The application of AI in the process of drug discovery may be a low risk setting from a regulatory perspective, as the risk of non-optimal performance often mainly affects the sponsor. 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 would normally be reviewed by the sponsor to mitigate ethical issues, risks of bias and other sources of

discrimination of non-majority genotypes and phenotypes from a data quality and quantity perspective (see Technical aspects – Data acquisition and augmentation).

2.2.2. Non-clinical development

AI/ML applications in non-clinical development may strive not only to achieve improved performance and robustness in data analysis, but could potentially also include AI/ML modelling approaches to replace, reduce, and refine the use of animals. Standard Operating Procedures (SOPs) would be expected to extend to all AI and ML applications in preclinical 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*.

Any preclinical data that is potentially relevant for assessment of the benefit-risk balance of a medicinal product should be analysed in accordance with a pre-specified analysis plan, prior to any data mining.

2.2.3. Clinical trials

2.2.3.1. Good clinical practice (GCP)

All requirements in the *ICH E6 guideline for good clinical practice (GCP)* or *VICH GL9 Good clinical practices (veterinary)* would be expected to apply to the use of AI/ML within the context of clinical trials. Of note, if a model is generated for clinical trial purposes, the full model architecture, logs from modelling, 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 should be made available for comprehensive assessment at the time of market authorisation or clinical trial application.

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 level of complexity of the trial, the use of decentralised elements, the intended use as a decision support software should be reflected in the specific protocol benefit-risk assessment.

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

Medical devices and *in vitro* diagnostics (IVDs) are regulated at 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, the following 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.

When using CE marked devices, fulfilment of additional requirements may be needed to qualify 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] 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)

See section 2.3 for reflections on regulatory interactions.

2.2.3.3. Data analysis and inference

When AI/ML models are used for transformation or analysis 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 Section 5) and include analysis of the impact on downstream statistical inference. In late-stage clinical development, this requires a detailed description of a pre-specified data curation pipeline and a fully frozen set of models used for inference, within the statistical analysis plan.

Early-phase clinical trials

Similar to drug discovery, risks in using AI/ML models for data analysis in early stages of clinical development are often low but can contain higher-risk applications affecting patient safety, 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, 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 opening of any dataset used for hypothesis testing, the data pre-processing pipeline and all models should be locked 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 open repository prior to their deployment in a pivotal clinical trial.

2.2.4. Precision medicine[4]

AI/ML can be used to individualize 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.

This would be regarded as a high-risk use from a medicines regulation perspective, related to both patient risk and level of regulatory impact. In addition to the principles spelled out elsewhere in this document for high-risk use cases, special care should be paid in defining what constitutes a change in

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

posology (requiring a regulatory evaluation before implementation), to provide guidance that the prescribers can critically apprehend, and include fall-back treatment strategies in cases of technical failure.

2.2.5. Product information

AI applications used for drafting, compiling, translating, or reviewing medicinal product information documents are expected to be used under close human supervision. Given that generative language models are prone to include plausible but erroneous 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.

2.2.6. Manufacturing

The use of AI/ML in the manufacturing of medicinal products including process design and scale up, 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. The EMA Quality Innovation Group is engaging actively with stakeholders in this field to come up with relevant recommendations for human and veterinary medicines.

2.2.7. 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, 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.

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.

2.3. 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 is 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 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. If development or use of a medicinal product is critically relying on information from a AI/ML medical device in accordance with Regulation (EU) 2017/745[5], or the information generated may be included in the Summary of product characteristics of an authorised medicinal product, early regulatory interaction is also recommended.

The documentation to inform the interaction with regulators should cover questions such as intended context of use, generalizability, performance, robustness, 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.

2.4. Technical aspects

2.4.1. Data acquisition and augmentation

AI/ML models are intrinsically data-driven, as they extract their weights from training data. This makes them vulnerable to the integration of human bias into models. All efforts should be made to acquire a balanced training dataset, considering the potential need to over-sample rare populations, and 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 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, and normalisation, 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. 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 generalizability 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.

[5] The note on medical devices in this context applies to human medicines only.

2.4.2. Training, validation, and test data

It should be noted that the term validation is used differently in the field of AI/ML and medicines development. It the field of 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. Once this process is completed, the 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 *de facto* becomes a second-stage validation data set and a completely new and independent test dataset is needed to repeat the test procedure for an updated model.

The practice of an early train-test split, prior to any normalisation or other types of processing where aggregated measures are used, is strongly encouraged. Even so, the risk of unintentional or 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 study outcomes on a global level can contain information that increases risk of overfitting the model. Hence, models intended for high-risk settings (in particular, non-transparent models intended for use in late-stage clinical development) should be prospectively tested using newly acquired data.

2.4.3. 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 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.

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

It is of particular importance to avoid overfitting, both in relation to the validation and test datasets. 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 and validation environment. This can occur both intentionally and unintentionally, as well as through indirect channels such as shared methods for data collection or processing that cannot be generalised to future context of use.

It is important to clearly describe the intended use of the model, to allow a validity assessment of the feature engineering. For example, baseline factors should generally be kept out of training data when building an individual case assessment model for clinical trial evaluation, as baseline correlations to outcome are often inherently insensitive to interventions.

2.4.4. Performance assessment

The choice of metrics for performance assessment is crucial for an adequate assessment of the model. In general, the set of metrics should contain parameters that are insensitive to class imbalances (such as the Matthews Correlation Coefficient) and describe the full confusion matrix. To identify random effects related to the train-test split, the distribution of performance metrics generated though 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. A priori defined thresholds for

performance metrics that can be related to the context of use further support the credibility of model performance.

2.4.5. Interpretability and explainability

To strengthen procedural fairness, accountability and prevention of bias, the use of transparent models is preferred, everything else being equal. However, it is acknowledged that several of the most effective modelling architectures allow only limited insight into the translation from feature space through latent space to prediction or classification. 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 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, methods within the field of explainable AI should be used whenever possible. This includes providing feature importance lists, *SHAP* and/or *LIME* analyses or similar explainability metrics, 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 attention plots to verify that features are extracted from relevant positions in the image or sequence.

2.4.6. Model deployment

Deployment of AI/ML models should be performed in line with the risk-based approach described for model development. For high-risk use cases, all non-trivial changes in the software and hardware stack supporting the model, including version changes for key dependencies, require a bridge re-evaluation of model performance. Similarly, it is 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 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, performance and compliance with applicable standards should be regularly evaluated, especially for autonomous incremental learning systems.

For all models, especially those where there is no human-in-the-loop, a risk management plan should be developed that defines likely risks of fail modes of the algorithm, e.g. what are the 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.

2.5. Governance

SOPs implementing GxP principles on data and algorithm governance should be extended to include all data, models and algorithms used for AI/ML throughout the medicinal product lifecycle. 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.

2.6. Data protection

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.

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 and freedoms, assess 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 anonymised or synthetic data or deploy differential privacy techniques. 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.

2.7. Integrity aspects

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 potentially 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 memorization due to their storage capacity. Overfitting increase the risk of memorization, while regularization, drop-out and addition of random noise can provide partial to complete anonymization, depending on the implementation.

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

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 are 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[6].

A systematic impact analysis should be conducted in the early stages of planning and development, and expertise on ethical and legal aspects should be onboarded early in all projects. 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 and 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 and pharmacovigilance.

However, the use of exceptionally great numbers of trainable parameters arranged in non-transparent model 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 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, refers to systems that display intelligent behaviour by analysing their environment and taking actions – with some degree of autonomy – to achieve specific goals.

[6] 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.

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.
CTA	Clinical Trial Application
Data leakage	Direct or indirect propagation of information from the intended test dataset to the model development environment.
Deep learning	The use of machine learning (see below) to train deeply stacked high-parameter models from data
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
High impact/risk setting	Use cases where errors have large consequences, e.g. related to the primary endpoint in a clinical trial or the physical safety of humans or animals.
IVDR	In Vitro Diagnostic Regulation (EU 2017/746)
Interpretability	The property to communicate 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 - an application of AI that enables systems to learn - i.e., models being trained - from data without being explicitly programmed.
Model	Mathematical algorithms with parameters (weights) arranged in an architecture that allows learning of patterns (features) from training data
Overfitting	Learning details from training data that cannot be generalised to new data
SHAP	Shapley Additive Explanations; an explainable AI (XAI) framework that can provide model-agnostic local explainability for tabular, image, and text datasets
Test dataset	The "hold-out" data that is used to estimate performance of the final ML model
Training dataset	The data used to train the ML model
Transformation	Change between different representations of data
Transparency	The possibility to fully trace information flow within a ML model
Validation dataset	The dataset used during model development, to inform on how to optimally train the model from training data.

5. Other 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)

- 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 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)

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)

6. References

This reference list is generally applicable, unless specific applicability to human or veterinary medicines is indicated.

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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)[7]

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)[8]

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6. European Commission High-Level Expert Group on AI <https://digital-strategy.ec.europa.eu/en/policies/expert-group-ai> (Accessed 24 May 2023)

7. European Commission High-Level Expert Group on AI, 'Assessment List for Trustworthy Artificial Intelligence (ALTAI) for self-assessment' (17 July 2020). <https://digital-

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

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

8. 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)

9. European Commission, 'Personalised medicine' <Personalised medicine (europa.eu)> (Accessed 15 June 2023)[9]

10. 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)[9]

11. International Coalition of Medicines Regulatory Authorities (ICMRA), 'Innovation' < https://icmra.info/drupal/strategicinitiatives/innovation> (Accessed 24 May 2023)[9]

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[10] Applicable to veterinary medicines only.