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5 **Reflection paper on the use of Artificial Intelligence (AI) in**
6 **the medicinal product lifecycle**
7 **Draft**

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

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44 **1. Introduction**

45 Data are generated and used increasingly across sectors, including those related to the lifecycle of
46 medicines. In the healthcare sector, data are captured in electronic format on a routine basis. The
47 utilisation of artificial intelligence (AI) - systems displaying intelligent behaviour by analysing data and
48 taking actions with some degree of autonomy to achieve specific goals - is an important part of the
49 digital transformation that enables increased use of data for analysis and decision-making. Such
50 systems are often developed through the process of machine learning (ML) where models are trained
51 from data without explicit programming. However, as these technologies often use exceptionally great
52 numbers of trainable parameters arranged in non-transparent model architectures, new risks are
53 introduced that need to be mitigated to ensure the safety of patients and integrity of clinical study
54 results. Also, as the overarching approach is inherently data-driven, active measures must be taken to
55 avoid the integration of bias into AI/ML applications and promote AI trustworthiness.

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

61 It is crucial to identify aspects of AI/ML that would fall within the remit of EMA or the National
62 Competent Authorities of the Member States as the level of scrutiny into data during assessment will
63 depend on this remit. This reflection paper focuses only on the use of AI in the medicinal product
64 lifecycle and any references to qualification of novel methodologies for medicines development¹,
65 interaction etc. are to be understood within this scope. However, medical devices with AI/ML
66 technology can be used within the context of clinical trials to generate evidence in support of a
67 marketing authorisation application and/or can be combined with the use of a medicinal product. In
68 such cases EMA will be involved in the assessment on whether the characteristics of the device is
69 adequate to generate evidence, supporting a EU marketing authorisation. Similarly, if a device is used
70 to provide recommendations in the Summary of Product Characteristics, e.g. on posology or
71 monitoring, the EMA will assess all relevant aspects of the proposed combined use.

72 This reflection paper describes the current experience of EMA in a field where scientific knowledge is
73 fast evolving. It should be read in coherence with both legal requirements and overarching EU
74 principles on AI, data protection, and medicines regulation (see references).

75 While some considerations in this reflection paper are of general interest for the development of
76 veterinary medicinal products, important differences exist between the human and veterinary domain
77 including legal bases, regulatory requirements and guidance, ethical issues, risks of bias and other
78 sources of discrimination. Further reflections will be necessary to better identify the specific
79 circumstances and sources of bias in the veterinary setting. While veterinary medicines regulated by
80 Regulation (EU) 2019/6 are generally within the scientific scope of this document, the reader is advised
81 to pay attention to notes pointing out fundamental differences. Specific veterinary reflections or
82 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 \(europa.eu\)](https://www.ema.europa.eu/en/qualification-of-novel-methodologies-for-medicine-development))

83 **2. Discussion**

84 **2.1. General considerations**

85 AI and ML tools can, if used correctly, effectively support the acquisition, transformation, analysis, and
86 interpretation of data within the medicinal product lifecycle. It should be noted that many
87 recommendations, best practices, and previous learnings within areas of model informed drug
88 development and biostatistics also apply to the field of AI/ML. Adjacent methodology guidelines which
89 may be relevant are listed in section 5 of this document.

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

93 Advice on risk management will be further reflected in future regulatory guidance, as the impact of
94 system malfunction or degradation of model performance can range from minimal to critical or even
95 life-threatening. The degree of risk may depend not only on the AI technology, but also on the context
96 of use and the degree of influence the AI technology exerts. In addition, the degree of risk may vary
97 throughout the lifecycle of the AI-system. Marketing authorisation applicants or marketing
98 authorisation holders (MAHs) planning to deploy AI/ML technology are expected to consider and
99 systematically manage relevant risks from early development to decommissioning.

100 If an AI/ML system is used in the context of medicinal product development, evaluation, or monitoring,
101 and is expected to impact, even potentially, on the benefit-risk of a medicinal product early regulatory
102 interaction such as qualification of innovative development methods for a specific intended use in the
103 context of research and development in relation to pharmaceuticals¹ or scientific advice is advised. The
104 level of scrutiny would depend on the level of risk and regulatory impact posed by the system.

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

110 For all requests for advice or opinions the applicant or MAH is expected to provide a scientific base
111 along with sufficient technical details to allow comprehensive assessment of any AI/ML systems used in
112 the medicinal product lifecycle, the integrity of data and generalizability of models to the target
113 population and for a specific context of use.

114 **2.2. AI in the lifecycle of medicinal products**

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

117 **2.2.1. Drug discovery**

118 The application of AI in the process of drug discovery may be a low risk setting from a regulatory
119 perspective, as the risk of non-optimal performance often mainly affects the sponsor. However, if
120 results contribute to the total body of evidence presented for regulatory review, principles for non-
121 clinical development (see below) should be followed. In this context, all models and datasets used
122 would normally be reviewed by the sponsor to mitigate ethical issues, risks of bias and other sources of

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

125 **2.2.2. Non-clinical development**

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

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

135 **2.2.3. Clinical trials**

136 **2.2.3.1. Good clinical practice (GCP)**

137 All requirements in the *ICH E6 guideline for good clinical practice (GCP)* or *VICH GL9 Good clinical*
138 *practices (veterinary)* would be expected to apply to the use of AI/ML within the context of clinical
139 trials. Of note, if a model is generated for clinical trial purposes, the full model architecture, logs from
140 modelling, validation and testing, training data and description of the data processing pipeline would
141 likely be considered parts of the clinical trial data or trial protocol dossier and thus should be made
142 available for comprehensive assessment at the time of market authorisation or clinical trial application.

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

147 **2.2.3.2. Use of medical devices and in vitro diagnostics in clinical trials**

148 Medical devices and *in vitro* diagnostics (IVDs) are regulated at according to the Regulation (EU)
149 2017/745 on Medical Devices (MDR) or Regulation (EU) 2017/746 on in vitro diagnostic medical
150 devices (IVDR). Applications within areas of medicines development and use can include an interplay
151 with such devices. Hence, the following section is provided for completeness and without prejudice to
152 the existing guidance on medicinal products used in combination with medical devices.

153 When AI/ML systems are used for clinical management of an individual patient, they may be
154 considered medical devices according to MDR or IVDR^{2,3}. Specific guidance on the Qualification and
155 Classification of Software within the framework of the MDR and IVDR can be found in MDCG 2019-11³.
156 It is not in the remit of the EMA to qualify or classify software under the above regulations.

157 When using CE marked devices, fulfilment of additional requirements may be needed to qualify for use
158 within the context of a clinical trial, to ensure the rights, safety, wellbeing of subjects, integrity of data
159 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 \(link\)](#)

160 See section 2.3 for reflections on regulatory interactions.

161 **2.2.3.3. Data analysis and inference**

162 When AI/ML models are used for transformation or analysis of data within a clinical trial of a medicinal
163 product, they are considered a part of the statistical analysis and should follow applicable guidelines
164 on statistical principles for clinical trials (see Section 5) and include analysis of the impact on
165 downstream statistical inference. In late-stage clinical development, this requires a detailed description
166 of a pre-specified data curation pipeline and a fully frozen set of models used for inference, within the
167 statistical analysis plan.

168 *Early-phase clinical trials*

169 Similar to drug discovery, risks in using AI/ML models for data analysis in early stages of clinical
170 development are often low but can contain higher-risk applications affecting patient safety, such as
171 treatment assignment or dosing. In all cases, measures should be taken to ensure that all estimates
172 used for planning of subsequent clinical trials are statistically robust and that exploratory analyses are
173 interpreted in relation to multiplicity. In circumstances where data from early-phase clinical trials may
174 have a substantial regulatory impact, such as in limited clinical development programs, requirements
175 may be higher and should be discussed through early regulatory interaction.

176 *Pivotal clinical trials*

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

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

186 If possible, it is encouraged that models are published in an open repository prior to their deployment
187 in a pivotal clinical trial.

188 **2.2.4. Precision medicine⁴**

189 AI/ML can be used to individualize treatment in relation to factors such as disease characteristics,
190 patient genotype, wide-band biomarker panels and clinical parameters. This could include patient
191 selection, dosing, *de novo* design of product variants and selection from a pre-manufactured library of
192 variants.

193 It is possible that an AI/ML application is referenced in the Summary of product characteristics to aid
194 such decisions on indication and posology. Without prejudice to the need for conformity assessment by
195 other regulatory bodies, the safety and efficacy of the medicinal product together with the AI-driven
196 application is a matter for medicines regulation.

197 This would be regarded as a high-risk use from a medicines regulation perspective, related to both
198 patient risk and level of regulatory impact. In addition to the principles spelled out elsewhere in this
199 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.

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

203 **2.2.5. Product information**

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

209 **2.2.6. Manufacturing**

210 The use of AI/ML in the manufacturing of medicinal products including process design and scale up, in-
211 process quality control and batch release is expected to increase in the coming years. Model
212 development, performance assessment and life-cycle management should follow the quality risk
213 management principles, taking patient safety, data integrity and product quality into account. For
214 human medicines the principles of ICH Q8, Q9 and Q10 should be considered, awaiting revision of
215 current regulatory requirements and GMP standards. The EMA Quality Innovation Group is engaging
216 actively with stakeholders in this field to come up with relevant recommendations for human and
217 veterinary medicines.

218 **2.2.7. Post-authorisation phase**

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

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

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

233 **2.3. Regulatory interactions**

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

239 Early interaction on experimental technology is provided by the EMA Innovation Task Force (ITF).

240 Scientific advice and qualification¹ of novel methodologies in medicines development is provided by the

241 Scientific Advice Working Party (SAWP) of the CHMP and Scientific Advice Working Party (SAWP) of the
242 CVMP. The term qualification advice/opinion refers to novel methodologies applied to medicinal product
243 development where the methodology to be qualified would ideally be medical device/software agnostic.

244 Timing of interactions should be guided by the regulatory impact and risk associated with using the AI
245 based models in context of the lifecycle of a medicinal product. In high-impact cases, interaction may
246 be crucial already at the planning stage. If development or use of a medicinal product is critically
247 relying on information from a AI/ML medical device in accordance with Regulation (EU) 2017/745⁵, or
248 the information generated may be included in the Summary of product characteristics of an authorised
249 medicinal product, early regulatory interaction is also recommended.

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

254 **2.4. Technical aspects**

255 **2.4.1. Data acquisition and augmentation**

256 AI/ML models are intrinsically data-driven, as they extract their weights from training data. This makes
257 them vulnerable to the integration of human bias into models. All efforts should be made to acquire a
258 balanced training dataset, considering the potential need to over-sample rare populations, and taking
259 all relevant bases of discrimination as specified in the EU principle of non-discrimination and the EU
260 fundamental rights into account. Dedicated reflections will be necessary to identify potential biases
261 applicable to veterinary medicines considering the difference e.g. in target populations and regulatory
262 requirements between veterinary and human medicines.

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

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

- 269 • relevance and population representativeness of data, and intra-/extrapolation assumptions
270 made,
- 271 • class imbalances and corresponding mitigation measures taken, and
- 272 • potential risk for unfair or discriminatory outcomes from using the data.

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

278 If limitations in the training dataset remain, affecting the generalizability or fairness of the model,
279 these should be clearly presented in the model documentation along with recommendations on the use
280 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.

281 **2.4.2. Training, validation, and test data**

282 It should be noted that the term validation is used differently in the field of AI/ML and medicines
283 development. In the field of ML, validation refers to the data used to inform on the selection of model
284 architecture and hyperparameter tuning and is hence part of the data driven process. Once this
285 process is completed, the performance of the model is evaluated once using the hold-out test data set.
286 If test performance is unsatisfactory and further model development is needed, the current test data
287 set *de facto* becomes a second-stage validation data set and a completely new and independent test
288 dataset is needed to repeat the test procedure for an updated model.

289 The practice of an early train-test split, prior to any normalisation or other types of processing where
290 aggregated measures are used, is strongly encouraged. Even so, the risk of unintentional or
291 unconscious data leakage cannot be completely excluded. For example, unknown case overlaps in
292 clinical databases, sponsor-specific basic features shared between study protocols or even general *a*
293 *priori* knowledge of study outcomes on a global level can contain information that increases risk of
294 overfitting the model. Hence, models intended for high-risk settings (in particular, non-transparent
295 models intended for use in late-stage clinical development) should be prospectively tested using newly
296 acquired data.

297 **2.4.3. Model development**

298 Given the plethora of modelling approaches and architectures, only generally applicable considerations
299 are provided on model development. It is the responsibility of the applicant or MAH to ensure that
300 SOPs promote a development practice that favours model generalisability and robustness - particularly
301 for settings where models cannot be updated during deployment - and to keep traceable
302 documentation and development logs to allow secondary assessment of development practices.

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

306 It is of particular importance to avoid overfitting, both in relation to the validation and test datasets.
307 Overfitting that is the result of non-optimal modelling practises is usually discoverable in the model
308 test phase. A more problematic cause of overfitting is data leakage from the test dataset into the
309 training and validation environment. This can occur both intentionally and unintentionally, as well as
310 through indirect channels such as shared methods for data collection or processing that cannot be
311 generalised to future context of use.

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

316 **2.4.4. Performance assessment**

317 The choice of metrics for performance assessment is crucial for an adequate assessment of the model.
318 In general, the set of metrics should contain parameters that are insensitive to class imbalances (such
319 as the Matthews Correlation Coefficient) and describe the full confusion matrix. To identify random
320 effects related to the train-test split, the distribution of performance metrics generated through cross-
321 validation should be presented. Sensitivity analysis for minority classes and in relation to calendar time
322 is expected, to support the generalisability to data with different class proportions, and robustness in
323 relation to uncontrolled secular trends in data at deployment. A priori defined thresholds for

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

326 **2.4.5. Interpretability and explainability**

327 To strengthen procedural fairness, accountability and prevention of bias, the use of transparent models
328 is preferred, everything else being equal. However, it is acknowledged that several of the most
329 effective modelling architectures allow only limited insight into the translation from feature space
330 through latent space to prediction or classification. The use of such *black box* models may be
331 acceptable in cases where developers substantiate that transparent (i.e., interpretable) models show
332 unsatisfactory performance or robustness. Model use should be supported by an underlying general
333 rationale and detailed information on model architecture, hyperparameter tuning, training metrics, as
334 well as validation and test results, along with a pre-defined monitoring and risk management plan for
335 mitigating non-transparency issues. It is recommended that such applications are discussed in detail
336 within the scope of an EMA qualification¹ or scientific advice procedure.

337 To allow review and monitoring, methods within the field of explainable AI should be used whenever
338 possible. This includes providing feature importance lists, *SHAP* and/or *LIME* analyses or similar
339 explainability metrics, both for the model and for individual inferences during deployment. Computer
340 vision models, and extensions into other modalities where attention mechanisms are used, should
341 whenever possible be supported by attention plots to verify that features are extracted from relevant
342 positions in the image or sequence.

343 **2.4.6. Model deployment**

344 Deployment of AI/ML models should be performed in line with the risk-based approach described for
345 model development. For high-risk use cases, all non-trivial changes in the software and hardware stack
346 supporting the model, including version changes for key dependencies, require a bridge re-evaluation
347 of model performance. Similarly, it is of importance that the data acquisition hardware, software, and
348 data transformation pipeline at inference is in line with pre-defined specifications.

349 Monitoring of model performance should be instituted to allow early detection of degradation and
350 thresholds for acceptable model performance should be clearly defined. This may include routine
351 sampling of data for manual classification or use of externally provided test data sets from external
352 quality control programs. Also, performance and compliance with applicable standards should be
353 regularly evaluated, especially for autonomous incremental learning systems.

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

358 **2.5. Governance**

359 SOPs implementing GxP principles on data and algorithm governance should be extended to include all
360 data, models and algorithms used for AI/ML throughout the medicinal product lifecycle. Aspects related
361 to the governance of all components used, the application of data protection and compliance with
362 applicable data protection laws and ethical standards should be documented and regularly reviewed.

363 **2.6. Data protection**

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

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

376 The necessity assessment should reflect on the possibility to use anonymised or synthetic data or
377 deploy differential privacy techniques. Otherwise, it should be justified why these options are not
378 feasible in view of the objectives pursued.

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

382 **2.7. Integrity aspects**

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

389 Large language models, often containing billions of parameters, are at particular risk of memorization
390 due to their storage capacity. Overfitting increase the risk of memorization, while regularization, drop-
391 out and addition of random noise can provide partial to complete anonymization, depending on the
392 implementation.

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

395 **2.8. Ethical aspects and trustworthy AI**

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

- 401 • Human agency and oversight
- 402 • Technical robustness and safety
- 403 • Privacy and data governance

- 404 • Transparency
- 405 • Accountability
- 406 • Societal and environmental well-being
- 407 • Diversity, non-discrimination, and fairness

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

410 To build trust in the effectiveness, reliability, and fairness of AI/ML tools, a human-centric approach
411 should guide all development and deployment of AI and ML. This requires not only that active
412 measures are taken during data collection and modelling (See Technical aspects) but also that both
413 user and patient reported outcome and experience measures are included in the evaluation of AI/ML
414 tools when they interface with an individual user or patient⁶.

415 A systematic impact analysis should be conducted in the early stages of planning and development,
416 and expertise on ethical and legal aspects should be onboarded early in all projects. In this regard,
417 applicants and MAHs are recommended to consider the Ethics guidelines for trustworthy AI by the
418 High-Level Expert Group on AI, set up by the European Commission.

419 **3. Conclusion**

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

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

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

435 **4. Glossary**

436 Definitions should be aligned with the definitions contained in the Regulation of the European
437 Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial
438 Intelligence Act) and amending certain Union legislative acts once this regulation has been finally
439 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.
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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.

440 5. Other methodology guidance

441 5.1. Guidance concerning human medicines

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

- 444 • The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for
445 Human Use (ICH):
 - 446 ○ 'Draft ICH guideline E11A on pediatric extrapolation Step 2b'
447 (EMA/CHMP/ICH/205218/2022) (6 April 2022) <[draft-ich-guideline-e11a-pediatric-
448 extrapolation-step-2b_en.pdf \(europa.eu\)](#)> (Accessed 26 May 2023)
 - 449 ○ 'ICH E9 Statistical Principles for Clinical Trials' (EMA/CPMP/ICH/363/96) (1 September
450 1998) <[E 9 Statistical Principles for Clinical Trials \(europa.eu\)](#)> (Accessed 26 May
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 - 452 ○ 'ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the
453 guideline on statistical principles for clinical trials' (EMA/CHMP/ICH/436221/2017) (17

- 454 February 2020) < [E9 \(R1\) Step 5 addendum on estimands and Sensitivity Analysis in](#)
455 [Clinical Trials to the guideline on statistical principles for clinical trials \(europa.eu\)](#)>
456 (Accessed 26 May 2023)
- 457 ○ 'ICH E10 Choice of control group in Clinical Trials' (EMA/CPMP/ICH/364/96) (1 January
458 2001) < [E 10 Choice of Control Group in Clinical Trials \(europa.eu\)](#)> (Accessed 26 May
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- 460 ○ 'ICH Q8 (R2) on pharmaceutical development' (EMA/CHMP/ICH/167068/2004) (22
461 June 2017) < [Q8 \(R2\) Step 5 Pharmaceutical Development \(europa.eu\)](#)> (Accessed 26
462 May 2023)
- 463 • European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) (formerly
464 The European Agency for the Evaluation of Medicinal Products Committee For Proprietary
465 Medicinal Products (CPMP)):
- 466 ○ 'Draft guideline on multiplicity issues in clinical trials' (EMA/CHMP/44762/2017) (15
467 December 2016) < [Guideline on multiplicity issues in clinical trials - for publication](#)
468 [\(europa.eu\)](#)> (Accessed 26 May 2023)
- 469 ○ 'Guideline on adjustment for baseline covariates in clinical trials'
470 (EMA/CHMP/295050/2013) (26 February 2015)' < [Guideline on adjustment for baseline](#)
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- 472 ○ 'Guideline on missing data in confirmatory clinical trials' (EMA/CPMP/EWP/1776/99
473 Rev. 1) (24 June 2010) <[guideline-missing-data-confirmatory-clinical-trials_en.pdf](#)
474 [\(europa.eu\)](#)> (Accessed 26 May 2023)
- 475 ○ 'Guideline on registry-based studies' (EMA/426390/2021) (16 September 2021)
476 <[Guideline on registry-based studies \(europa.eu\)](#)> (Accessed 26 May 2023)
- 477 ○ 'Guideline on reporting the results of population pharmacokinetic analyses'
478 (CHMP/EWP/185990/06) (21 June 2007) <[Guideline on Pop PK reports - Adopted](#)
479 [\(europa.eu\)](#)> (Accessed 26 May 2023)
- 480 ○ 'Guideline on the investigation of subgroups in confirmatory clinical trials'
481 (EMA/CHMP/539146/2013) (31 January 2019) <[Guideline on the investigation of](#)
482 [subgroups in confirmatory clinical trials \(europa.eu\)](#)> (Accessed 26 May 2023)
- 483 ○ 'Points to consider on application with 1. Meta-analyses; 2. One pivotal study'
484 (EMA/CHMP/EWP/2330/99) (31 May 2001) <[Points to consider on application with 1.](#)
485 [meta-analyses; 2. one pivotal study \(europa.eu\)](#)> (Accessed 26 May 2023)
- 486 ○ 'Reflection paper on methodological issues in confirmatory clinical trials planned with
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488 [on Methodological Issues in Confirmatory Clinical Trials Planned with an Adaptive](#)
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490 **5.2. Guidance concerning veterinary medicines**

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

- 493 • The International Cooperation on Harmonisation of Technical Requirements for Registration of
494 Veterinary Medicinal Products (VICH):

- 495 ○ 'VICH GL9 on good clinical practices (CVMP/VICH/595/98-FINAL) (4 July 2000)
- 496 <[VICH Topic GL9 \(GCP\) \(europa.eu\)](#)> (Accessed 20 June 2023)
- 497 • European Medicines Agency Committee for Veterinary Medicinal Products (CVMP):
- 498 ○ 'Guideline on statistical principles for clinical trials for veterinary medicinal products
- 499 (pharmaceuticals)' (EMA/CVMP/EWP/81976/2010-Rev.1) (15 July 2021) <[GL on](#)
- 500 [statistical principles for clinical trials for VMPs \(pharmaceuticals\) \(europa.eu\)](#)>
- 501 (Accessed 20 June 2023)
- 502 ○ 'Guideline on clinical trials with immunological veterinary medicinal products'
- 503 (EMA/CVMP/IWP/260956/2021) (19 January 2021) <[Guideline on clinical trials with](#)
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- 530 7. European Commission High-Level Expert Group on AI, 'Assessment List for Trustworthy
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