EU GMP Annex 22: AI Compliance in Pharma Manufacturing

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Executive Summary

The pharmaceutical industry is undergoing a rapid transformation driven by advanced *artificial intelligence* (AI) technologies. In response, the European Medicines Agency (EMA), together with the PIC/S (Pharmaceutical Inspection Co-operation Scheme), has introduced **Annex 22 "Artificial Intelligence"** as a new appendix to the EU GMP (Good Manufacturing Practice) guidelines. This draft annex – published for stakeholder consultation on 7 July 2025 – is the first comprehensive regulatory framework on AI specifically for the manufacture of medicinal products and active substances ([1] meritsolutions.com) ([2] picscheme.org). It significantly extends existing computerized systems requirements (e.g. Annex 11) by adding AI-specific rules. Key provisions include unrewarded use of *"static, deterministic"* machine learning models in critical applications (learning/adaptive and probabilistic models are prohibited), strict explainability and performance requirements for AI systems, rigorous data management, thorough validation, and continuous monitoring (including fallback routing to human operators) ([3] www.scribd.com) ([4] meritsolutions.com). Crucially, Annex 22 mandates that any AI-based decision affecting patient safety, product quality, or data integrity must perform at least as well as the validated manual process it replaces ([5] www.scribd.com) ([4] meritsolutions.com). The annex draws a clear line between **critical AI** (safety/quality/data-critical tasks) – which must meet these high standards – and **non-critical AI** (support tasks) – where generative models or LLMs may be used but under mandatory human supervision ([6] meritsolutions.com) ([7] gmpinsiders.com). In practice, the new rules require manufacturers to implement multi-disciplinary governance, complete documentation and traceability, data integrity (ALCOA+) for AI data, and robust vendor oversight. Industry experts emphasize early preparation: companies must inventory all AI use-cases, classify risk levels, document current process performance baselines, and fill gaps in explainability and controls ([8] meritsolutions.com) ([9] gmpinsiders.com). Real-world case studies – from predictive maintenance to AI-integrated visual inspection – demonstrate the technology's promise but also underscore that full GMP compliance (with validation and audit trails) is achievable and essential ([10] www.covasyn.com) ([11] www.covasyn.com). This report provides an in-depth analysis of Annex 22, explaining its background, key requirements, practical compliance checklist, and broader implications for pharmaceutical manufacturing regulation.

Introduction and Background

The European Union's *EudraLex*, Volume 4 (the **EU GMP Guide**), has long been the authoritative standard for pharmaceutical quality and manufacturing. Traditional GMP annexes (e.g. Annex 11 on Computerised Systems, Annex 15 on validation, Annex 16 on release) were written in the pre-AI era and do not fully address emerging machine learning technologies. As AI and machine learning (AI/ML) systems become integrated into processes – from process control to quality assurance – regulators have aimed to update these guidelines. Annex 22 fills this gap by specifically targeting AI used in GMP-critical manufacturing environments ([2] picscheme.org) ([1] meritsolutions.com).

The need for such regulation is driven by the *transformative power of AI*. AI and ML tools are now widely adopted across industries: for example, a 2025 KPMG survey found that 66% of people use AI regularly, and 83% believe AI will bring broad benefits ([12] kpmg.com). In pharma, AI is applied in drug discovery, diagnostics, and increasingly in manufacturing and quality control ([13] www.pharmout.net). PharmOut notes that AI enables "predictive maintenance" in production equipment and real-time anomaly detection in quality control, leading to improved batch consistency and reduced waste ([14] www.pharmout.net). Yet, pharmaceutical manufacturing is fundamentally regulated to protect patient safety and product quality. As AI makes decisions that directly influence critical attributes, regulators insist that its use must be carefully controlled.

The regulatory landscape is evolving. In mid-2024 the EU enacted the EU AI Act (Regulation (EU) 2024/1689), a broad law governing AI across sectors. However, Annex 22 is a **sector-specific** guidance focused on AI in GMP environments. Like the EU AI Act for consumer and industrial AI, Annex 22 reflects a risk-based approach: only high-impact AI (those affecting safety, quality, or data integrity) triggers the strictest requirements ([15] meritsolutions.com) ([2] picscheme.org). In

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July 2025, PIC/S and the European Commission opened a joint consultation on the draft revisions to Chapter 4 (Documentation), Annex 11 (Computerised Systems), and the new Annex 22 (AI) ([2] picscheme.org) (health.ec.europa.eu). The regulatory aim is a **global alignment**: Annex 22 was drafted by the EMA's Inspectors' Working Group in collaboration with PIC/S, with the FDA and UK MHRA participating as observers ([16] meritsolutions.com). EMA/PIC/S emphasize this harmonization, noting that the updated Annex 22, together with the revised Chapter 4 and Annex 11, will provide a "comprehensive and robust framework [for] IT technologies in pharmaceutical manufacturing while safeguarding product quality and patient safety" ([17] picscheme.org) (health.ec.europa.eu).

By effectively becoming the *"Annex 11 for AI"*, Annex 22 is set to become the legal and operational standard for AI in European GxP manufacturing ([1] meritsolutions.com) ([18] gmpinsiders.com). It is a six-page addition to EudraLex V4 (Draft published 7 July 2025) that "sets the first comprehensive regulatory expectations for the use of AI in GxP environments" ([1] meritsolutions.com).The draft is undergoing public consultation through October 2025, with final adoption expected in 2026 and enforcement phased in by 2027–2028 ([19] meritsolutions.com). In this context, European pharma manufacturers must prepare now: the following sections analyze the full content and compliance implications of Annex 22, drawing on official synopses and expert interpretations.

Scope of Annex 22

Annex 22 is **highly targeted**: it applies only when AI/ML models are used *within* computerised systems that play a **critical** role in manufacturing of active substances or medicinal products – i.e. in tasks with direct impact on patient safety, product quality, or data integrity ([20] www.scribd.com) ([21] gmpinsiders.com). It does *not* apply to trivial AI uses (e.g. administrative chatbots) or to computer systems without embedded AI. In effect, Annex 22 sits on top of Annex 11: all AI models are still part of regulated computerised systems (Annex 11), but Annex 22 adds AI-specific expectations for those models when they take on critical decision-making tasks ([22] gmpinsiders.com) ([2] picscheme.org).

Importantly, Annex 22 distinguishes **critical** from **non-critical** AI use. *Critical AI* is defined as any model whose output directly influences GMP-sensitive decisions. These are subject to the full Annex 22 regime: only *static, deterministic* models are permitted, and they must meet stringent performance and validation criteria. *Non-critical AI* (e.g. drafting documents, internal assistance, data visualization) can include dynamic or generative models, but only if a qualified human remains "in the loop" to oversee outputs ([6] meritsolutions.com) ([7] gmpinsiders.com). Both PIC/S and industry commentators explicitly forbid using **adaptive or generative AI in critical roles**. For example, the draft clarifies that **dynamic learning models** ("models which continuously and automatically learn and adapt performance during use") are **not covered** by Annex 22 and "should not be used in critical GMP applications" ([3] www.scribd.com). Likewise, **probabilistic outputs** (where identical inputs may yield different results) are excluded. Most notably, **Generative AI and large language models (LLMs)** – by design probabilistic and uncontrollable – "should not be used in critical GMP applications" ([23] www.scribd.com) ([7] gmpinsiders.com). In contrast, if LLMs or generative tools are used in *non-critical* settings, strict human oversight is mandated: a competent person must validate outputs and maintain records ([24] www.scribd.com) ([25] gmpinsiders.com).

In summary, Annex 22 *only* applies to AI cases where static, deterministic ML models are embedded in a GMP computerised system and are used in safety/quality-critical applications. Everything else is either outside scope (legacy software with fixed logic), or allowed only under Annex 11 and company procedures with human review. This narrow scope focuses regulators on the highest-risk AI use-cases, ensuring that truly "probabilistic" or continuously learning systems (and complex LLMs) cannot quietly creep into core quality processes without strict controls.

Key Requirements and Principles

Annex 22 enshrines several foundational GMP principles applied to AI systems. First, **personnel and governance**: Manufacturers must assemble cross-functional teams (QA, process experts, IT, and data scientists) when developing or

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implementing AI models ([26] www.scribd.com) ([9] gmpinsiders.com). All individuals must have clearly defined responsibilities, appropriate qualifications, and training for their role. The draft emphasizes that "relevant parties" work together on algorithm selection, training, validation, testing and operation ([26] www.scribd.com). Quality oversight cannot be siloed off: for example, PIC/S commentary stresses that "AI systems are not exempt from GMP controls" and actually *require enhanced* diligence in governance due to their complexity ([27] gmpinsiders.com). In practice, this means updating quality management systems and SOPs to explicitly cover AI development, assignment of an "AI owner," and regular governance meetings (e.g. change boards) that include data science input.

Second, **documentation and traceability** are paramount. Annex 22 demands that every aspect of the AI lifecycle be recorded, just as for any other validated system. All activities – from model design through testing and deployment – "must be documented, regardless of whether performed internally or outsourced" ([28] gmpinsiders.com). Key items include specifications of intended use, data sources, model parameters, version history, and review records. In effect, Annex 22 reinforces the ALCOA+ principles for AI data: every decision must be *Attributable* and *Traceable*. Vendors and software suppliers must provide documentation on their AI algorithms (architecture, training procedures, etc.), and manufacturers must retain audit logs of model changes, training runs, and user interactions. The key is that nothing about the AI process is a "black box" in the quality records: as GMPInsiders notes, "All activities related to the AI model, including training, validation, and testing, must be documented" ([28] gmpinsiders.com).

Third, **risk management** underpins the annex. Every AI application must have a documented *intended use* and a justified risk assessment. Annex 22 explicitly requires that the AI model's **purpose and tasks** be defined and approved before testing begins ([29] gmpinsiders.com). This means writing down, for example, "This neural network classifies tablet coating defects on the production line." Each intended use must reference the process details, data characteristics, and risk factors (e.g. types of outliers or bias). Regulators stress that Annex 22's requirements scale with risk: in high-impact cases, elaborate controls (strict metrics, monitoring, human review) are mandatory. As one expert summary states, *"the level of oversight and control should correspond to the potential impact on patient safety, product quality, and data integrity."* ([30] gmpinsiders.com). Thus, manufacturers should perform a risk assessment (consistent with ICH Q9) for each AI use-case, and use it to inform the extent of validation and review documented in the AI quality plan.

Technical and Operational Requirements

Annex 22 contains numerous specific controls that mirror standard validation but with AI nuances. These can be grouped under **Data & Model Management**, **Validation & Testing**, and **Operation & Monitoring**.

Data Quality and Separation. AI depends critically on data. Annex 22 requires managers to ensure high-quality, representative datasets for training and testing. *Training Data Quality*: Training datasets must cover the full range of expected process variability, with no missing extreme cases. They must be unbiased and well-documented ([31] qmsdoc.com). The annex emphasizes that *"the quality, completeness, and representativeness of data used as training data"* is essential ([31] qmsdoc.com). *Data Security & Governance*: Since AI may handle sensitive manufacturing and IP data, entries must be secure (access controls, encryption) and logged ([32] qmsdoc.com). *Data Separation*: Crucially, training, validation, and test datasets must be completely separate to avoid data leakage. Test data must never overlap with the training inputs ([33] qmsdoc.com). Annex 22 explicitly notes that any data used for testing should not have been used in training "at all" ([34] qmsdoc.com). In practice, this means rigorous data partitioning and, preferably, third-party checks on data splits. Each data set (training, test, and any holdout) should be archived with provenance and version tracking to meet ALCOA+ standards ([35] qmsdoc.com).

Model Testing and Validation. Annex 22 places at least as much emphasis on model validation as on development. Prior to deployment, a comprehensive **test plan** must be executed. This starts with defining clear *performance metrics* aligned to intended use: for example, a classification model might be evaluated by sensitivity, specificity, precision, accuracy, or F1-score as appropriate ([36] www.scribd.com). Managers must then set **acceptance criteria** for those metrics *before any testing begins*. A key novel requirement is *performance equivalence*: the model's acceptance thresholds must

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equal or exceed the performance of the process it replaces. In other words, an AI batch release check must be at least as effective as the historical manual check it automates ([5] www.scribd.com). The draft explicitly states: *"The acceptance criteria of a model should be at least as high as the performance of the process it replaces"* ([5] www.scribd.com). This drives companies to precisely quantify the current human/process performance baseline and to prove the AI model can match or outperform it.

During testing, independent verification is mandated. The annex calls for test execution with data entirely disjoint from the training set, verified labeling, and double-checking critical test results. For example, handwritten or image data must be annotated by multiple experts to ensure labeling accuracy ([37] www.scribd.com). Any deviation from the test plan or failure to meet criteria must be thoroughly documented, investigated, and resolved ([38] www.scribd.com). All test records (including raw data, code runs, metrics) must be retained. Staff involved in validation (both data scientists and QA approvers) must sign off on the report, much as in a traditional IQ/OQ process.

Explainability and Confidence. For *critical AI*, Annex 22 insists on transparency. Models must be interpretable so that each key output can be understood by experts. The use of opaque "black-box" models (e.g. unconstrained deep neural networks without any explainability) is discouraged. Specific measures are required: during testing, techniques like feature-attribution should be used to demonstrate *why* a model made a given decision, and those results must be reviewed by process SMEs ([39] www.scribd.com). The guidance even suggests including external explainability tools (e.g. "agnostic local explainability" heuristics) for datasets like images or text where needed ([40] www.scribd.com).

In operation, each model decision must carry an associated "confidence score". The draft states that the system **should** provide a confidence estimate whenever possible. Manufacturers must also define a *confidence threshold*: if a model's confidence in a prediction falls below this threshold, the output must be flagged for human review or be routed to a fallback process. This matches the industry expert guidance that "uncertain" outputs should be automatically sent back to a qualified person ([4] meritsolutions.com). The threshold itself must be justified in validation (e.g. show that below 95% confidence accuracy drops unacceptably). Thus, explainability and confidence-scoring are built into the heart of Annex 22's expectations: models can only be relied on if they are both understandable and accountable.

Operation and Monitoring. Annex 22 also imposes controls on live use. Once validated and deployed, AI models must not be "set and forgotten". The annex requires continuous change control and monitoring of model performance over time (health.ec.europa.eu) ([41] www.scribd.com). For example, the guidance explicitly demands *"continuous oversight"* including model performance monitoring and defined procedures for human review when necessary ([2] picscheme.org). In practice, manufacturers must periodically run the model on control datasets or 'shadow' data and check that the defined performance metrics remain stable. If performance degrades (e.g. due to drift in raw materials or operating conditions), the model must be revalidated. All model updates (including retraining with new data) must themselves follow change control processes, documenting why the update was done and how it was verified.

Finally, as with all GMP systems, access control is essential. Annex 22 reaffirms that role-based permissions must be enforced: only authorized personnel may train, modify, or operate the AI system ([28] gmpinsiders.com). Audit trails should capture user actions (who changed model parameters, who approved releases) ([42] gmpinsiders.com). In summary, a deployed AI model effectively becomes a controlled GMP system, with the added needs of continuous data science verification.

AI Compliance Checklist for Manufacturers

Based on Annex 22 and expert guidance, pharmaceutical companies should address the following compliance checkpoints when using AI in manufacturing:

Compliance Task	Key Requirement
Inventory AI Use-Cases	Identify all current and planned AI/ML systems in manufacturing (including vendor software) ([8] meritsolutions.com) ([2] picscheme.org). Classify each as *critical* (affecting safety/quality/data integrity) or *non-critical* to determine applicable controls ([15] meritsolutions.com) ([7] gmpinsiders.com).

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Compliance Task	Key Requirement
Define Intended Use	For each AI model, document the specific task, process context, data characteristics and risk justification ([29] gmpinsiders.com) ([36] www.scribd.com). Obtain SME/QP review and approval of the intended use before testing.
Governance Structure	Establish a multi-disciplinary team (QA, process experts, data scientists, IT) with defined roles ([26] www.scribd.com) ([9] gmpinsiders.com). Ensure management accountability and regular oversight (e.g. change control board involvement) in AI projects.
Model Type Compliance	Verify that any AI used in *critical* functions is a **static, deterministic** model (no continuous learning during use) ([3] www.scribd.com) ([6] meritsolutions.com). Prohibit use of adaptive, continuously-learning algorithms or generative AI/LLMs in critical processes ([3] www.scribd.com) ([24] www.scribd.com). (Non-critical uses may allow LLMs, but only with strict human review［12］.)
Data Quality & Separation	Ensure training data is high-quality and representative of real process variability ([31] qmsdoc.com). Rigorously separate datasets: no overlap of training, validation, and test data ([35] qmsdoc.com). Maintain records of dataset provenance, labeling checks (independent verification as needed ([37] www.scribd.com)), and ALCOA+ compliance ([31] qmsdoc.com).
Define Metrics & Acceptance	Select suitable performance metrics (e.g. accuracy, sensitivity, etc.) tied to intended use ([36] www.scribd.com). Establish quantitative **acceptance criteria** in advance, requiring model performance ≥ the existing manual process ([5] www.scribd.com) ([43] www.scribd.com). Document subgroup criteria if applicable.
Model Validation	Execute full validation per Annex 11 and Annex 22. Use separate test data (never previously used in training). After validation, document outcomes in a final report. Record any deviations (all must be investigated and justified ([38] www.scribd.com)). Ensure results trace to the GMP product specification.
Explainability and Confidence	For critical models, demonstrate interpretability (e.g. feature-attribution analysis) as part of validation ([39] www.scribd.com). Define and document a confidence threshold: any prediction below threshold must default to human review ([4] meritsolutions.com). Ensure logs capture reasons for low-confidence flags.
Change Control & Monitoring	Implement formal change control for any model update or retraining. Continuously monitor model performance on new production data ([41] www.scribd.com). Schedule periodic re-validation or recalibration if key metrics drift. Maintain audit logs of any modifications or retraining events.
Human Oversight (HITL)	If the AI output supports (but does not make) a decision, explicitly define the human role in SOPs ([44] www.scribd.com) ([25] gmpinsiders.com). Ensure operators are trained for this use case. Track human review: flows for low-confidence outputs and final accountability remains with the skilled person ([45] gmpinsiders.com).
Documentation & Traceability	Document *all* AI-related workflows: model architecture, hyperparameters, training logs, version histories, testing protocols, raw results, etc. Ensure records are maintained "like any manual process", with retained audit trails ([28] gmpinsiders.com) ([46] qmsdoc.com). This includes documenting QA oversight and approvals at each stage.
Vendor and IT Controls	Where AI software is procured or outsourced, ensure contracts/quality agreements assign validation and change management responsibilities clearly ([47] qmsdoc.com). Audit vendors for compliance. Confirm the AI system meets Annex 22 requirements before release.
Personnel Training	Train relevant staff not only on GMP principles, but also basic AI and data science concepts, ensuring *AI literacy*. QA/Audit functions should understand ML risks. The annex suggests that personnel have "adequate qualifications" for AI tasks ([26] www.scribd.com).
Quality Risk Management	Integrate all of the above into the company's Risk Management system. Update QRM documents (e.g. risk assessments, control plans) to reflect AI-related hazards, mitigation measures (HITL checkpoints, fallback decisions), and review them periodically tied to Annex 22 expectations ([30] gmpinsiders.com).
Regulatory Alignment	Prepare for inspection by mapping AI controls to Annex 22 language. For global operations, harmonize with other AI/ML regulations (e.g. US FDA guidances on AI/ML, EU AI Act). Document in advance how Annex 22 requirements are met to demonstrate compliance during audits or authorities' reviews.

Each item in this checklist draws directly from Annex 22 text and expert interpretation. For example, the requirement to **separate test and training data** and **document every step** is explicitly mentioned in the draft guidelines ([48] qmsdoc.com) ([28] gmpinsiders.com). The obligations for **defined governance, traceability, and risk-based oversight** are likewise emphasized by EMA/PIC-S and quality authorities ([28] gmpinsiders.com) ([2] picscheme.org). By systematically addressing the items above, a manufacturer can build a structured AI risk control program consistent with the expected regulations.

Case Studies and Examples

While Annex 22 is new, several real-world examples illustrate both the promise of AI in pharma manufacturing and the necessity of rigorous compliance.

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- **Continuous Manufacturing AI**: A recent *Journal of Pharmaceutical Sciences* analysis describes eight AI case studies in continuous production ([49] www.sciencedirect.com). These included soft sensor estimation of tablet potency, hybrid NIR-process control systems, advanced model-predictive control (MPC), and automated anomaly detection in downstream chromatography. In one case, an AI-driven monitor identified feedstock shifts earlier than traditional control charts. Importantly, this study highlights that *"organizations have to create data monitoring systems that provide thorough tracking with complete traceability"* for AI to be sustainable ([50] www.sciencedirect.com). In other words, each AI solution needed integrated GxP metrics and audit logs. These cases reflect a range of AI archetypes (monitoring, decision-support, optimization, inspection) and all underline Annex 22's emphasis on data integrity and quality system integration.

- **Quality Control Automation**: In the DACH (Germany/Austria/Switzerland) pharmaceutical market, consultants at CovaSyn report concrete use-cases in final quality inspection ([10] www.covasyn.com) ([51] www.covasyn.com). For example, a mid-sized tablet manufacturer implemented an AI-powered camera system (CNN) to automate visual inspection of tablets. The result: defect detection accuracy rose from 94% to **99.7%**, and false positives dropped by 60% ([52] www.covasyn.com). This translated into a 7-month payback on the ~€100k system. In a specialty chemicals plant, an AI anomaly detector monitored 47 process parameters and flagged emerging deviations; in six months it prevented 9 out-of-spec (OOS) batches (avoiding roughly €340,000 in losses) ([51] www.covasyn.com). Another case involved a generics manufacturer where an AI tool automatically pulled batch test results from LIMS and draft-composed release reports, cutting per-batch QP release time from 4 hours down to 45 minutes ([53] www.covasyn.com).

Strikingly, **all three CovaSyn projects were validated and GMP-compliant**. The article emphasizes that each implementation (<€100k investment) included full validation documentation and audit trails ([11] www.covasyn.com). The consistent lesson: small, well-scoped pilots can yield high ROI *and* meet regulatory standards. According to CovaSyn, starting with clearly defined use-cases and only scaling after proving value were key success factors ([54] www.covasyn.com). These examples show that when Annex 22-like rigor is applied (validated models, training documentation, human checkpoints), AI can dramatically enhance throughput and quality in practice.

- **Process Analytical Technology (PAT) Cases**: In academic settings, case studies of AI-powered soft sensors demonstrate Annex 22 principles. For instance, neural-network models have been created to predict tablet potency online. When evaluated, these models often require equivalent or superior accuracy to lab testing to be accepted. Researchers note that implementing such models demands "thorough tracking with complete traceability" – exactly the mandate of Annex 22 ([50] www.sciencedirect.com). Downstream bioprocessing experiments have similarly shown AI detecting chromatogram anomalies. Each study underlines the need for robust data separation and exact performance measurement. These real-world R&D cases align with Annex 22's core tenets: AI models in manufacturing cannot live outside the pharmaceutical quality system.

Tables and checklists from regulators often mirror these case lessons. For example, quality experts contrast *traditional validation* (Annex 11) with *AI model validation*, noting that the latter relies on training data patterns and demands extra controls like confidence scoring and explainability ([42] gmpinsiders.com). Likewise, Annex 22's stress on risk management and oversight resonates with GMPInsiders' chart of AI foundational principles, which includes the point that AI "systems are not exempt from GMP controls" and in fact "require enhanced diligence" ([27] gmpinsiders.com). In sum, while AI can augment efficiency and quality, every successful implementation we've identified has included careful adherence to rigorous documentation, validation and monitoring – foreshadowing the compliance checklists manufacturers must now adopt.

Implications and Future Directions

Annex 22's arrival marks a significant shift in pharmaceutical regulation. By explicitly regulating AI, European authorities acknowledge both the **potential benefits and risks** of machine learning. For manufacturers, the implications are multifaceted:

- **Quality Culture and Skills**: Companies must evolve their quality systems to include AI expertise. This means hiring or training data scientists, updating SOPs, and educating QA/auditors about AI principles. Annex 22 effectively forces pharma quality professionals to become *AI literate*. In the future, job roles like "AI compliance officer" or "digital quality manager" are likely to emerge. Some experts note that adopting Annex 22 early could be a competitive advantage: firms that integrate AI governance proactively will both satisfy regulators and reap operational gains sooner ([8] meritsolutions.com).

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- **Regulatory Alignment**: Annex 22 is expected to become a de-facto global standard. Its development with PIC/S, FDA/MHRA observers, and many countries signing PIC/S means that harmonization is intended ([16] meritsolutions.com) ([17] picscheme.org). Other regulatory bodies (e.g. Japan's PMDA, China's NMPA) often follow PIC/S revisions. Thus, companies confidently compliant with Annex 22 provisions may face fewer surprises internationally. However, differences may remain: for instance, outside Europe, some authorities might focus on AI within medical devices or drug development rather than process manufacturing. Future conferences will dissect how Annex 22 intersects with the EU AI Act (which categorizes, e.g., some medical systems as "high-risk"), but Annex 22 is more prescriptive for process AI. It does not replace the EU AI Act; rather, it operates in parallel for manufacturing-specific scenarios.

- **Technological Evolution**: Today's static/deterministic restriction may not hold indefinitely. Annex 22 bans continuous self-learning and generative AI in core processes, but these technologies are advancing rapidly. In the next 5–10 years, if stable, well-understood approaches to online learning emerge, regulators might revisit these rules. For example, *continuous validation frameworks* (FDA is also exploring change control for AI in devices) could one day allow certain adaptive models. Similarly, LLMs or generative systems may become more controllable; Annex 22 already allows them in non-critical roles with human oversight. In the future, we might see *Annex 23* or later revisions addressing narrowed scopes for advanced AI, especially as explainability tools improve.

- **Industry Best Practices**: Annex 22 codifies many practices that are already considered best-in-class. Its emphasis on risk-based QRM is consistent with ICH Q9/Q10, meaning AI links naturally into existing pharma quality systems. It encourages trends like *digital twins* and *in silico quality systems*, where AI continuously learns from production data (albeit periodically, not continuously by itself). It also dovetails with data integrity initiatives (ALCOA+) by extending principles to AI-produced data ([31] qmsdoc.com) ([46] qmsdoc.com). In sum, Annex 22 will likely accelerate the ongoing *data-first culture* in pharma.

- **Checklists and Standardization**: Practically, firms will create Annex 22 checklists (like the one in this report) and validation templates. Training programs and vendor qualification questionnaires will incorporate Annex 22 language. MasterControl and other software vendors are already promoting "AI-enhanced GMP compliance" platforms ([55] www.mastercontrol.com). Over time, one can envision standard Annex 22 certification processes or even inspections solely focused on AI systems. Some academic proposals suggest formal auditing of AI algorithms (akin to GLP for labs) – Annex 22 moves us partway in that direction by insisting on traceability of model versions, data sets, and personnel decisions.

The **patient safety** imperative underlies all these changes. By demanding that AI systems be at least as well understood and reliable as the manual methods they supplement, Annex 22 aims to prevent catastrophic failures (e.g. an AI falsely accepting an out-of-spec batch). It also protects manufacturers: by following clear rules, they gain predictable pathways to "audit-ready" AI use. The upcoming enforcement timeline (2027-28) gives firms time to adapt, but proactive work will be necessary. Ongoing dialogue between industry and regulators (through feedback on the draft, and later via workshops) will also shape practical implementation guidelines.

Conclusion

EU GMP Annex 22 represents a watershed in pharmaceutical regulation: it is the first major guideline explicitly covering AI in manufacturing. By doing so, it ensures that patient safety, product quality and data integrity remain protected in an era of advanced analytics and machine intelligence. The annex is comprehensive – from requiring multidisciplinary teams, rigorous data governance, and full validation, to explicitly forbidding uncontrolled AI in core tasks ([24] www.scribd.com) ([6] meritsolutions.com). Its focus on "intended use, defined metrics, continuous oversight" ([2] picscheme.org) mirrors fundamental GMP values.

As this report demonstrates, compliance with Annex 22 is a matter of thorough preparation. Firms should use the above checklist to guide internal audits and projects. They should treat each AI use-case as they would any critical GxP process: specify it clearly, validate it rigorously, and document it exhaustively ([29] gmpinsiders.com) ([5] www.scribd.com). Although the new rules add workload, numerous case studies show that AI can deliver significant benefits *and* be made fully GxP-compliant ([11] www.covasyn.com) ([50] www.sciencedirect.com). In the long run, Annex 22 is likely to strengthen the trustworthiness of AI in pharma, enabling innovative efficiencies while safeguarding the core mission of drug safety and efficacy.

References: Regulatory texts and guidance from EMA and PIC/S ([17] picscheme.org) (health.ec.europa.eu); industry analyses and news reports ([1] meritsolutions.com) ([10] www.covasyn.com); and peer-reviewed studies of AI in pharma

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manufacturing ([56] www.sciencedirect.com) ([50] www.sciencedirect.com) have been cited throughout. These sources provide the authority behind each compliance requirement and illustrate how Annex 22 will be applied in practice.

External Sources

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Regulatory Excellence: Only US AI consultancy with comprehensive FDA, EMA, and 21 CFR Part 11 compliance expertise for pharmaceutical drug development and commercialization.

Founder Excellence: Led by Adrien Laurent, San Francisco Bay Area-based AI expert with 20+ years in software development, multiple successful exits, and patent holder. Recognized as one of the top AI experts in the USA.

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Custom CRM Development: Build tailored pharmaceutical CRM solutions, Veeva integrations, and custom field force applications with advanced analytics and reporting capabilities.

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Custom ERP Development: Design and develop pharmaceutical-specific ERP systems, inventory management solutions, and regulatory compliance platforms.

Big Data & Analytics: Large-scale data processing, predictive modeling, clinical trial analytics, and real-time pharmaceutical market intelligence systems.

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Contact founder Adrien Laurent and team at https://intuitionlabs.ai/contact for a consultation.

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