



# Validating Intelligent Automation Systems in Pharmacovigilance: Insights from Good Manufacturing Practices

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## Abstract

Pharmacovigilance is the science of monitoring the effects of medicinal products to identify and evaluate potential adverse reactions and provide necessary and timely risk mitigation measures. Intelligent automation technologies have a strong potential to automate routine work and to balance resource use across safety risk management and other pharmacovigilance activities. While emerging technologies such as artificial intelligence (AI) show great promise for improving pharmacovigilance with their capability to learn based on data inputs, existing validation guidelines should be augmented to verify intelligent automation systems. While the underlying validation requirements largely remain the same, additional activities tailored to intelligent automation are needed to document evidence that the system is fit for purpose. We propose three categories of intelligent automation systems, ranging from rule-based systems to dynamic AI-based systems, and each category needs a unique validation approach. We expand on the existing good automated manufacturing practices, which outline a risk-based approach to artificially intelligent static systems. Our framework provides pharmacovigilance professionals with the knowledge to lead technology implementations within their organizations with considerations given to the building, implementation, validation, and maintenance of assistive technology systems. Successful pharmacovigilance professionals will play an increasingly active role in bridging the gap between business operations and technical advancements to ensure inspection readiness and compliance with global regulatory authorities.

## 1 Introduction

Pharmacovigilance is the science of monitoring the effects of medicinal products to identify and evaluate potential adverse reactions and provide necessary and timely risk mitigation measures [1]. It is a discipline that is heavily reliant on data, and benchmark data indicate that most pharmacovigilance departments of pharmaceutical companies dedicate a large proportion of their resources to processing adverse event (AE) cases, and the number of AE cases increases annually [2, 3].

Intelligent automation technologies have strong potential to automate routine work and balance resource use across safety risk management and other pharmacovigilance activities [4]. Intelligent automation can contribute to the quality and consistency of case processing and assessment, leading to a timely assessment of safety signals. When such technology solutions are implemented to assist in processing AE cases, regulations require pharmaceutical companies to validate this software [5].

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### Key Points

With the widespread adoption of technology in the pharmacovigilance space, pharmacovigilance professionals must understand and guide the building, validation, and maintenance of artificial intelligence (AI)-based pharmacovigilance systems. This is essential to ensure inspection readiness as we integrate automation systems across the pharmacovigilance value chain.

Intelligent automation systems can be grouped into three categories: rule-based static systems, AI-based static systems, and AI-based dynamic systems. Validation frameworks currently exist for rule-based static systems but not AI-based systems.

We propose validation considerations for a risk-based approach to compliant GxP AI-based static systems, which can be implemented within the good automated manufacturing practices framework.

Computerized system validation (CSV) is the process of establishing and documenting that the specified requirements of a computerized system are fulfilled consistently from design until decommissioning of the system and/or transition to a new system. The approach to validation should focus on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results [6].

Algorithms and rule-based software, electronic workflows, and pattern matching have been used widely in pharmacovigilance for years [4]. More recently, several companies and vendors have implemented robotic process automation to assist with the management of individual case safety reports (ICSRs). Such technologies follow existing guidance from regulators and industry guidelines such as the International Society for Pharmaceutical Engineering *Good Automated Manufacturing Practices Guide* (ISPE GAMP® 5) on the validation of computerized systems [7].

More recently, novel areas of research based on artificial intelligence (AI) technologies have evolved, including machine learning (ML) and natural language processing (NLP) techniques, and are now being adopted to support pharmacovigilance processes [8–10]. Although these types of technology show great promise with their capability to learn based on data inputs, existing validation frameworks may need to be augmented to verify intelligent automation systems. While the underlying validation requirements

largely remain the same (e.g., such as conformity with user specifications, traceability of decision points with an audit trail, and reliability of algorithm output), additional software development activities tailored to intelligent automation are needed to document evidence that the system is fit for purpose.

This paper presents a proposed classification of automation systems for pharmacovigilance, along with validation considerations for emerging technologies to support whether existing validation frameworks can be used or should be extended to constitute a reasonable/risk-based validation strategy, as has been done for computerized systems elsewhere within the industry [5, 7]. The primary focus of this paper is validation rather than other adoption considerations and potential barriers to implementation. This paper considers the use of intelligent automation solutions for pharmacovigilance, specifically for high-effort activities such as ICSR case processing [10]. The principles proposed may be applied to different areas that are subject to regulatory oversight.

## 2 Classification of Intelligent Automation Systems in Pharmacovigilance

Because existing validation frameworks may be sufficient for some novel technologies but not for others, there is a need for a classification of intelligent automation systems and the best-suited validation framework for each. Table 1 provides a breakdown of the types of automated pharmacovigilance (sub-) systems, some of the underlying technologies used within them, and examples of their application to pharmacovigilance processes.

In the classification (Table 1), the term “artificial intelligence” or AI is used to describe the simulation of human intelligence processes by computer systems but excludes purely rule-based systems. AI encompasses a wide range of technologies, including ML, text recognition, NLP, and machine translation. The considerations and elements described in this paper apply to supervised learning systems, within which the training data are curated and known by the model developers and subject matter experts [11].

For each classification of AI systems, the availability of a validation framework is categorized as established, emergent, or eventual (Table 1). “Established” frameworks are those for which clear guidance exists to support validation efforts. With “emergent” frameworks, a foundation exists but is insufficient for demonstrating fit-for-use systems within today’s regulated environment. No validation framework yet exists for “eventual” systems. The focus of our research is to

**Table 1** Classification of automated pharmacovigilance systems

Classification	Definition	Status/validation framework
Rule-based static systems	Automation is achieved via static rules designed to obtain the desired outcome Examples include expedited reporting rule configuration, auto coding, and robotic process automation for case intake	Status: established Validation framework: exists today
AI-based static systems	System configuration includes components that are AI informed but subsequently "frozen," i.e., systems based on AI or ML that do not adapt in production (after "go-live"). These are also called "locked" models Re-training of the model is not applied automatically and is limited to the occurrence of events/triggers that require modification (e.g., the output needs change, expansion of training data set to improve quality) Examples include an auto-translation system of source documents and a model based on ML for causality assessment of individual case safety reports	Status: emergent Validation framework: existing frameworks can be extended to cover these systems
AI-based dynamic systems	System configuration includes components that are AI informed and can adjust their behavior based on data after initial implementation in production, using a defined learning process [11] These are like AI-based static systems but are continually updated once in production, based on a set cadence or trigger, to include new source data. These systems are sometimes referred to as online algorithms	Status: eventual Validation framework: more thorough review of validation frameworks will be needed to cover these systems

AI artificial intelligence, ML machine learning

propose an extended validation system for AI-based static systems.

We based our classification of automated pharmacovigilance systems in Table 1 on the main ways people typically interact with data. The primary purpose was to identify considerations for validation of automation systems. We recognize this is an evolving area, and there may be a need to define additional classes in the future.

### 2.1 Validation of Artificial Intelligence (AI)-Based Systems Require Considerations Beyond Those Needed for Rule-Based Systems

Compared with rule-based systems, AI-based systems do not consist of a set of pre-defined rules but generally include models derived from a training data set (e.g., supervised ML based on "ground truth") or more generalized modeling of a "human-like" capability (e.g., auto-translation, NLP).

The potential advantages of AI-based systems are that more complex associations and patterns sometimes unknown to humans can be considered by a model, resulting in greater flexibility and ability to handle variable input (e.g., NLP for the handling of unstructured text).

However, the use of AI introduces some potential challenges related to the validation of these systems (Sect. 3.2).

### 2.2 Validation of AI-Based Static vs. AI-Based Dynamic Systems

Dynamic systems are those in which new data (e.g., newly received ICSRs) are used to continually update the model for future data, in contrast to static systems that use batch learning techniques that generate the model by learning on the entire training data set at once. A dynamic system is referred to as "online ML" or an "online adaptive system."

Such systems will dynamically adapt to new patterns in data and should proactively improve over time; however, they also introduce potential risks in terms of stability and performance of the model over time.

As these systems are inherently dynamic in nature, current validation and change control guidelines are no longer adequate to demonstrate consistent and reliable system performance. Moreover, some AI algorithms do not learn in a deterministic way, which adds additional validation challenges when such algorithms are not restricted to a static state. This reality will again require decisions regarding any re-validation over time.

To date, electronic systems utilized in pharmacovigilance are almost exclusively static. Dynamic systems may be used more frequently in the future when appropriate methods for timely validation of these systems become available and if the benefits of using a dynamic system outweigh the potential risks associated with these systems.

### 3 Validation Considerations for AI-Based Static Systems

#### 3.1 Validation Frameworks—ISPE GAMP® 5

Multiple frameworks exist to support CSV. Validation of rule-based static systems is well-established and supported by existing standards and industry guides, as described in ISPE GAMP® 5 [7]. Figure 1 illustrates the ISPE GAMP® 5 general approach to achieving computerized system compliance and fitness for use with any type of AI system. This approach can be applied both for initial system validation and subsequently as part of change control. However, some other considerations are covered in this paper.

The level of detail at each stage should be commensurate with the complexity. The model described in Fig. 1 is not the only potential framework for validation. However, it is the most widely adopted methodology in pharmacovigilance and is based on a scientific, risk-based approach. Therefore, we consider the ISPE GAMP® 5 methodology to be a seminal work and describe best practices for rule-based systems based on the ISPE GAMP® 5 approach. This also allows for AI functionality to be more easily accommodated within existing (validated) systems.

#### 3.2 Proposed ISPE GAMP® 5 Methodology for AI-Based Static Systems in Pharmacovigilance

To address the best practices as outlined for customized AI systems in pharmacovigilance (Fig. 2), we propose layering

the AI approach within the ISPE GAMP® 5 methodology, as shown in Fig. 3. Steps and deliverables are highlighted below and focus on data selection, model training and testing, validation, system testing, and monitoring.

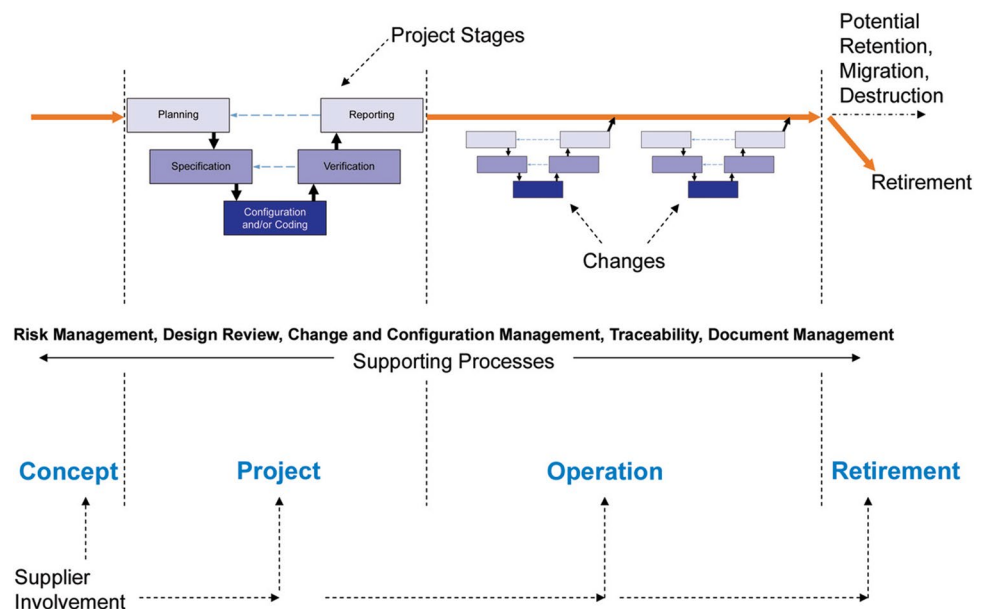
Table 2 describes considerations specific to the validation of AI-based static systems in each of the steps in Fig. 3 and potential techniques and approaches that could be used to address some challenges specific to AI-based static systems. For more general validation considerations, refer to either the ISPE GAMP® 5 guidance or other recommendations for agile models [7, 12]. For AI-based static systems that require initial training, we also consider the “good machine learning practices” framework and terminology introduced by the US FDA to be a seminal work [13].

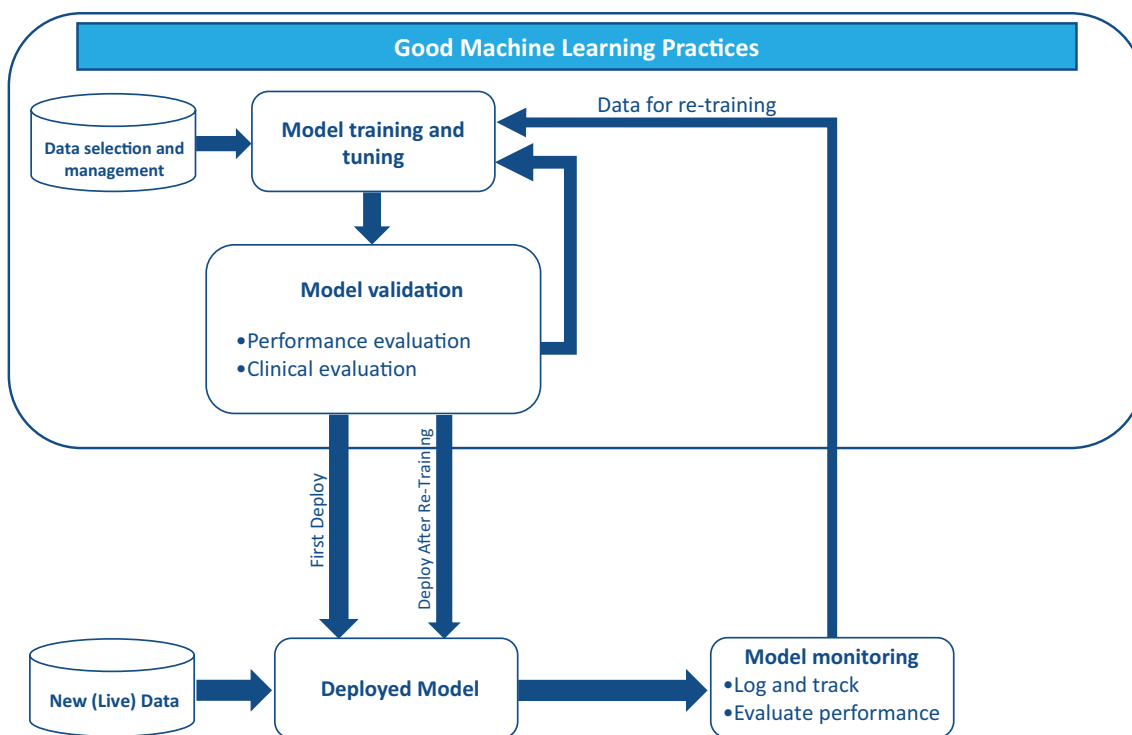
#### 3.3 Documentation Considerations for AI-Based Static Systems

Confidence in the output of AI-based static systems requires insight into why decisions are made within the model. Documentation regarding how the model was developed is a good way to provide insight into which considerations were taken during the development process.

We are proposing more specific documentation to be considered. This does not mean all forms of documentations are recommended for every model but rather for the documentation to be applied where it is appropriate, as documentation requirements also depend on the complexity of the system. The last column in Table 2 includes a proposal of the specific documentation that could be considered for AI-based static systems.

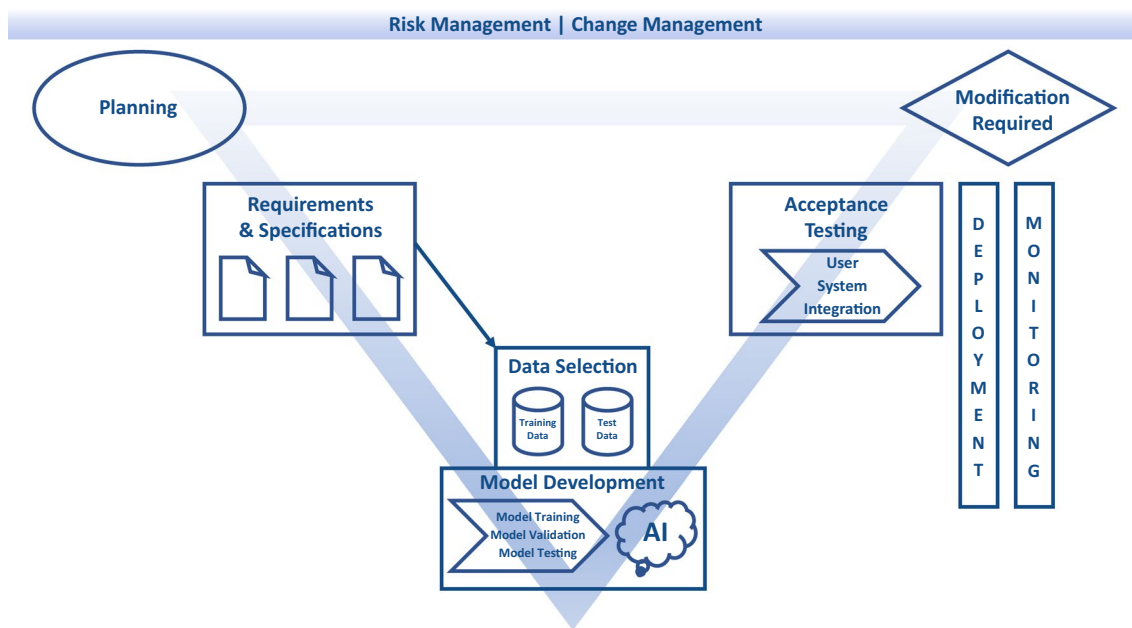
**Fig. 1** A General Approach for Achieving Compliance and Fitness for Intended Use (ISPE). Source: Figure 4.1, GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems, © Copyright ISPE 2008 [7]. All rights reserved. <https://www.ISPE.org>. Used with permission from ISPE (ISPE GAMP® 5, Figure 4.1)





**Fig. 2** Overlay of the US FDA’s total product lifecycle approach on artificial intelligence/machine learning workflow. Source: US FDA Proposed Regulatory Framework for Modifications to Artificial Intel-

ligence/Machine Learning (AI/ML)—based software as a Medical Device (SaMD), Discussion Paper and Request for Feedback, 2019 [13]



**Fig. 3** Proposed ISPE GAMP® 5 methodology for validating artificial intelligence (AI)-based static systems in pharmacovigilance

**Table 2** Validation considerations for artificial intelligence-based static systems

Area	Potential challenges when validating AI-based static systems using existing frameworks	Considerations for extending existing frameworks for AI-based static systems	Documentation considerations
Planning	The validation approach and strategy require careful planning	Gather knowledge and create the overall approach for validating an AI-based static system in the organization (master strategy, validation framework, etc.). The overall approach should refer to examples, best practices, templates, etc. Define performance thresholds and fallback plans/BCPs The activity scope will vary based on whether you are validating a new AI-based static system or adding an AI functionality within an existing validated system	The master strategy for AI-based static systems should include guidelines for the objective, scope, key activities, BCP/fallback plan, responsibilities, and acceptance criteria
Risk management	New and unknown types of errors and risks areas may not be considered in existing validation frameworks: Data and Environments Knowledge and Experience Complexity Availability Trust Regulations	New types of risk may need to be considered, or existing risk types may be emphasized. At a minimum, these risks need to be assessed individually for each system and mitigated appropriately Risks related to the quality of data include potential biases, completeness, sources, etc. Inaccuracies in the model due to production data changes over time ("model drift") There may be conditions within which the model works and those in which it does not (i.e., the operating envelope) Systemic rather than random errors may occur for fully automated systems, potentially introducing a bias Additional risks related to a system not reaching 100% accuracy, which may require additional assessment External vendor/supplier involvement Critical activity, downtime, or any other implications related to a deficiency in the model Required level of transparency/explainability of decisions versus required accuracy Existing risk identification and mitigation methodologies such as failure modes effect and criticality analysis could still be used	New risk categories can be incorporated into existing risk documentation deliverables (e.g., vendor risk assessment, functional risk assessment) A separate deliverable focusing on data risk assessment may be introduced or incorporated within existing documents

Table 2 (continued)

Area	Potential challenges when validating AI-based static systems using existing frameworks	Considerations for extending existing frameworks for AI-based static systems	Documentation considerations
Requirements and specifications	Performance metrics must be proactively defined with consideration given to the system's intended use.	<p>An acceptable performance level may be driven by the intended use of the system.</p> <p>Define the intended use and criticality of each individual component of the system (note: The system could be a combination of any automated and manual activities)</p> <p>Important risk-based considerations may be the impact (and quality) of targeted automation step(s) on the overall outcome of the process and the intended degree of automation. A good understanding is needed for cases where the system is effective vs. where it is not (i.e., consider the criticality of misses)</p> <p>Specific requirements may need to be included for exception flagging with respective confidence scores to facilitate performance verification during validation</p>	<p>Desired performance level can be defined using different metrics and is not necessarily limited to a level of accuracy</p> <p>The most appropriate measure may consist of a combination of criteria (e.g., overfitting to manage false positives vs. false negatives when predicting case validity)</p>
Data selection	AI-based static systems are dependent on data selection, whereas existing validation frameworks are dependent on process	<p>The methodology for the data collection, selection, and cleaning, should consider the following aspects:</p> <ul style="list-style-type: none"> <li>Collection of data representative of the process, ensuring correct distribution among the data classes, categories, or labels</li> <li>Assignment of "ground truth"</li> <li>Data quality, completeness, and lifetime accuracy considerations</li> <li>Close collaboration amongst pharmacovigilance professionals and technical experts</li> <li>Allow models to handle new categories in production, ensure a small sample training set contains instances with an "unknown" category</li> <li>Data used for training and validation of the model should be independent of and separate from the test data</li> <li>Frequent updates of the test data set to ensure it is not stale and remains representative of the sample population</li> <li>Ensure that the test data set receives the same data pre-processing treatments applied to training data</li> <li>Ensure the model does not rely on personal identification or other irrelevant fields for making predictions</li> </ul>	<p>Data selection and preparation approach, covering: Audit and sequestration of training/validation and test data</p> <ul style="list-style-type: none"> <li>Collection protocols</li> <li>Reference standard determination</li> <li>Quality assurance</li> <li>Data pre-processing</li> </ul>

Table 2 (continued)

Area	Potential challenges when validating AI-based static systems using existing frameworks	Considerations for extending existing frameworks for AI-based static systems	Documentation considerations
<p><i>Model development</i> (model build, train and test, model validation) Note: "Model validation" refers to the definition used in ML – see footnote</p>	<p><i>Model training, selection, and validation</i> (see footnote) Training, selection, and validation of an AI model is a new and delicate process</p>	<p>Training of AI models requires a combination of expertise in AI/ML with a deep understanding of the data and related process Best practices for model training (i.e., good ML practices) need to be integrated into the validation framework Utilize pre-trained models and transfer learning, where possible, as these methods are proven to be less sensitive to implicit biases in the data Utilize techniques that lower any potential bias, e.g., regularization, dropouts, and cross-validation Define the methodology to assess model performance using an independent team to avoid bias (e.g., blinding) Study the basic metrics (including precision, recall, accuracy, and F-score) to define model performance</p>	<p>A test planning, strategy, and evaluation plan, including the following: Model selection (e.g., protocol, rationale, and experimentation for the choice of model) Adherence to good ML practices Validation protocol (methodology, splitting strategy)</p>
<p><i>Model testing</i></p>	<p>It is not usually possible to list and test all potential scenarios that are handled by such a model</p>	<p>A tailored approach to testing (e.g., statistical and risk-based blinding methodology) and test environment(s) is typically necessary Test model performance on incomplete, missing, delayed, corrupt, noisy, invalid, and unknown data points</p>	<p>A test planning, strategy, and evaluation plan, including the following: Test planning and strategy (methodology and test environment(s)) Evaluation plan (metrics definition, acceptance thresholds) Versioning performance records Specific test data inclusion</p>
<p><i>Model explainability and traceability</i></p>	<p>Need transparency in how the AI model arrived at a certain decision</p>	<p>Careful model designing should be implemented to maintain a clear understanding of the models in any instance As part of the design phase, consideration should be given to the required level of transparency and explainability concerning how the AI model arrived at a decision. There could be a trade-off in that more complex AI models involving deep learning may have a higher degree of accuracy but are inherently less transparent in how a decision was made [14]. Where complex models are used, then it should be possible for someone to describe broadly how the system is working and the principles used for decision making, and any boundaries beyond which the system is not trained Avoid the "Black box" effect</p>	<p>Ensure complete documentation of the AI model at each version Document ML architecture, hyper-parameters, and parameters</p>



Table 2 (continued)

Area	Potential challenges when validating AI-based static systems using existing frameworks	Considerations for extending existing frameworks for AI-based static systems	Documentation considerations
Acceptance testing	<p>The integration of an AI model into the entire system (user interface, dashboards, reports, interfaces) may be a challenging activity</p>	<p>Specialized resources trained in both testing and the business area are essential to verify acceptance and the intended use of the entire system</p> <p>The AI model can work as intended, but the acceptance level of testing should verify its integral performance</p> <p>Planning of respective levels of integration testing and acceptance testing may require advanced test techniques (e.g., unit testing, integration, test automation, security, usability, etc.)</p> <p>Consider the latest approaches (e.g., US FDA's CSA) [15]</p> <p>Test model roll-back capability in case of an error in production</p>	<p>Test strategy and planning should consider: Validation of the AI model vs. entire system acceptance testing</p> <p>Test types and techniques</p> <p>Risk-based testing (CSA)</p> <p>Model rollbacks</p>
	<p>Address the impact of external intervention on monitoring performance of the model</p>	<p>Quality control activities and measurements for model performance must be inserted at points in which the findings will be representative of the model and not representative of the model combined with potential external intervention</p> <p>Monitoring approaches for AI-based static systems:</p> <p>Concurrent activities of the model, along with the historical approach, allow for comparison, adjudication, and identification of potential performance issues</p>	<p>Test strategy and planning should consider: Validation of the AI model vs. entire system acceptance testing</p> <p>Test types and techniques</p> <p>Risk-based testing (CSA)</p> <p>Model rollbacks</p>

Table 2 (continued)

Area	Potential challenges when validating AI-based static systems using existing frameworks	Considerations for extending existing frameworks for AI-based static systems	Documentation considerations
System deployment and monitoring	<p>Although training data should be representative of the real world, training data cannot be exhaustive, may be limited, may exclude a rare scenario, or may not be representative of all situations</p> <p>Post-deployment monitoring and early detection of model performance degradation are critical to maintaining expectations from a regulatory and business perspective</p>	<p>Pre-defined robust monitoring plan with periodic quality control measures is recommended. Strong consideration must be given to the perceived level of risk and potential impact of performance degradation on the quality and integrity of the entire system</p> <p>Various circumstances can trigger model changes: quality standards/thresholds not being met, an opportunity to create new ground truth improving model performance, change in data input, or a change in business or regulatory requirements. The monitoring plan should include the threshold and criteria for (1) when thresholds are not met and (2) when to consider a root cause or impact assessment</p>	<p>Monitoring plan with pre-established: Periodicity Performance metrics Acceptable quality standards and thresholds Investigation measures to understand and isolate the root cause of performance degradation</p> <p>Retraining plan with defined triggers for retraining (e.g., suboptimal performance for three straight periods) Criteria for implementation of optimized models into production</p>
Change management	<p>Appropriately challenge performance. Understand model capabilities and limitations to avoid potential bias of assuming accuracy, which can result in reliance on a model with suboptimal performance</p> <p>Version control of an AI model is based on specific training data and is a part of the entire system (also version controlled)</p>	<p>When evaluating a potential missed scenario, it is important to understand whether a given scenario was included within the scope of the training material or whether it is an entirely new scenario</p> <p>The model may occasionally require retraining, and the reasons for this retraining should be documented as they arise</p> <p>Consider a retrained model as a new model independent from the previous versions. All model versions should be recorded and documented for reproducibility and audit purposes</p> <p>Apply software change management principles when there is a need for end-to-end system change. This should be separate from changes to the ML subcomponents</p> <p>Consider using tools to build AI models that allow for version control (i.e., model management platforms)</p>	<p>The change should be documented, including objectives of the change; models and features should be version controlled</p> <p>All versions should be recorded and documented for reproducibility and audit purposes. Track model parameters, training dataset, and algorithm details for each model version</p> <p>The quality plan must be evaluated for potential changes (e.g., changes in parameters or configuration) that may require modification over time</p>

Specific document requirements will be dependent on system complexity and intended use. In machine learning, model validation is the process in which a trained model is evaluated with a testing data set. The main purpose of using the testing data set is to test the generalization ability of a trained model [16]. Visit TransCelerate's website for more detail [17]

AI artificial intelligence, *BCPs*'s business continuity plans, *CSA* computerized system assurance, *ML* machine learning

## 4 Conclusions

New and existing intelligent automation systems have great promise for enhancing existing processes in pharmacovigilance. In this article, we introduced a categorization of automation subsystems. Depending on the category, validation methodology may already be well-understood (e.g., rule-based static systems) or may pose significant unknowns (e.g., AI-based dynamic systems).

Traditional validation methodologies can be extended to cover AI-based static systems. The main points to highlight for AI-based static systems are as follows:

- Risk assessment within an overall risk-based approach will be crucial to defining the level of validation activities needed.
- New deliverables are being introduced to cover ML (e.g., data acquisition plan and model test plan).
- Data quality is a key consideration.
- Monitoring after deployment in production is critical and should be an essential consideration of the validation approach.
- Terminology alignment is necessary for a good understanding of the meaning between CSV specialists, business users, and ML experts.
- Close collaboration amongst pharmacovigilance professionals and technical experts is required.

As this technology area is still evolving quickly, best practices for validation of these systems will continue to emerge and evolve. AI-based static systems may be implemented more frequently in the future, including, perhaps, even some dynamic elements. Our validation considerations applied to the GAMP validation framework and support opportunities for increasing the adoption of intelligent automation technologies within pharmacovigilance by offering the industry a framework for developing these technologies. In time, best validation practices for these technologies can be identified and evaluated against the goal of enhanced patient safety. Future research will focus on the development of AI-based dynamic systems, for which the considerations must address the continuous learning nature of these systems.

Alignment with regulators on validation is critical to the implementation of AI-based systems within the highly regulated pharmacovigilance industry. As part of this alignment process, industry should engage regulators actively in discussions since agreement on high-level performance measures with a clear interpretation and verifiable measurement processes will be essential.

Pharmacovigilance professionals must learn new skills and acquire technical knowledge relating to system implementation and CSV to remain successful in this rapidly

advancing sector [18]. A once-siloed working paradigm is shifting, requiring pharmacovigilance professionals to understand business and technical requirements, to select representative data to adequately train and approve AI models, and to understand how, when, and why to retrain their models over time. A deep understanding of AI is becoming more closely intertwined with pharmacovigilance operations and will dictate which pharmacovigilance functions will successfully leverage assistive technology to further consistency in data collection and evaluation, ultimately improving compliance and positive outcomes for our patients globally.

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## Declarations

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**Consent for publication** Not applicable.

**Availability of data and materials** Not applicable.

**Code availability** Not applicable.

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