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# Automated Classification of Post-Approval Changes Using Regulatory Intelligence Models

**Kiran Kumar Gande ***

*Quagen Pharmaceuticals, Fairfield, US*

## Abstract

Post-Approval Changes (PACs) further introduce an immense regulatory burden and sometimes result in long approval times and conflicting categorizations across different countries. We processed 7,500 PACs with 47.7% minor, 48.7% moderate, and 3.7% major changes. For this study, the machine learning algorithms of Gradient Boosting, Random Forest, SVM, and Logistic Regression were trained on 16 regulatory features varying from clinical impact, quality risk, and explanation of quality scores. Gradient Boosting was found to have the highest accuracy of 87.3% for classification, surpassing traditional classification methods and minimizing discrepancies in approval times. For quality scores with high justification, approval times were reduced by 23%, and major changes took an average of 287.5 days as opposed to 156.7 days for minor changes. Such automated platforms have the potential to save 60%–75% of time spent on manual classification methods and allow real-time API connectivity with regulatory intelligence systems. The automated classification results of PACs have a vast potential for scaling up the consistency of regulations, improving approval times, and laying the foundation for global harmonization in post-approval change management.

**Conclusion:** The machine learning-driven classification of post-approval changes has shown good predictive capability, and the results demonstrate the achievement of reductions in the regulatory approval time. This substantiates the feasibility of the incorporation of regulatory intelligence with the use of AI systems for the achievement of harmonization

**Keywords:** Post-approval changes; regulatory intelligence; machine learning; pharmaceutical regulation; automated classification; regulatory compliance

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*Corresponding author. E-mail address: sriramakkgebgc825@gmail.com (G.K.Kumar).

## 1. Introduction

The pharmaceutical industry is operated under a highly regulated environment where post-approval changes of approved drug products are tightly controlled by international health authorities. These changes, from change of manufacture up to change of formulation are a vital matter of maintaining product integrity and providing space for ever-better enhancement and innovation. (1) Traditional post-authorization change management is highly reliant on manual processes that are ever increasingly unacceptable within the realities of globalized pharma supply chains and explosion of volume of regulatory data. (2) Systematic identification of regulatory information, processing and interpreting it and taking advantage of it and making strategic business decisions is one of the pharmaceuticals' key strengths. (3) Online convergence of artificial and machine learning technologies and regulatory intelligence systems has unprecedented ability of laborious steps of automation of classification, compression of processing time and streamlining of regulatory submission consistency. (4) Implementation of these systems must, however, seriously be considered against regulatory adoption, validation requirements, and inherent complexity of regulatory decision-making processes. (5)

Current post-authorization of change management processes is hampered by several issues. ICH Q12 guidelines provide a checklist of post-authorization changes but unevenly implemented within regions of regulatory control. (6) Without harmonized change classification criteria, uneven evaluations, longer intervals of approvals, and greater drug manufacturer cost of compliance follow. (7) Moreover, manual practice of the current processes results in bottlenecks that can negatively impact drug supply and patient access to drugs. (8) This development of artificial intelligence is a paradigm shift from reactive regulatory governance to predictive regulatory governance. (9) Machine learning technologies are able to read vast databases of past regulatory filings, discerning patterns within the outcomes of approvals, and

constructing predictive change classification models. (10) They are capable of transforming the post-authorization change management from the laborious practice of the manual approach to data-driven streamlined practice.

### 1.1 Post-Approval Change Regulatory Framework

The post-approval change regulatory system has seen remarkable changes in the past years because of the need to reconcile innovation and patient protection. The ICH Q12 guideline is one of the important milestones toward the harmonization of post-approval change management, with guidelines of product life cycle management and change control strategy. Classification of post-approval changes has been received differently by local regulatory authorities, where the United States Food and Drug Administration (FDA) has put changes under annual report changes, changes being effected (CBE) and prior approval supplement (PAS) category and the European Medicines Agency (EMA) by a three-level classification. (11)

Post-approval change authorization lead times were quantitatively estimated based on recent business surveys and were found to vary globally from three to five years and excessively long periods of quality enhancements and product optimizations. (12) This is because regulatory requirements and authorization lead times vary between countries and lead to inventory segregation, supply chain complications, and additional costs. It is an indicator of the need for more harmonized and efficient processes of change management after post-approvals.

### 1.2 Artificial Intelligence in Regulatory Affairs

Pharmaceutical regulatory affairs saw the arrival of artificial intelligence when the FDA unveiled its Center for Drug Evaluation and Research (CDER) AI Council in 2024. (13) Numerous FDA guidance has featured the use of AI in drug development and artificial intelligence of regulatory decision-making enablement of drug and biologic products. (14) Machine learning regulatory affairs solutions span a continuum of use cases ranging from document processing, regulatory intelligence, pharmacovigilance, and submission readiness. Application of AI within regulatory processes do require special effort toward ensuring the interpretability, validation, and acceptability of the regulator. (15) Regulators are highly dependent on assuring transparency and explainability of AI decision-making processes. "Good Machine Learning Practice" has been put forward as the best practice of ensuring proper and effective AI deployment within highly regulated industries with a special focus on good validation, regular monitoring, and proper human oversight.

### 1.3 Regulatory Intelligence Systems

Regulatory intelligence systems have progressed from static data warehouse stores to intelligent real-time monitoring, analyzing, and forecasting. Web crawled ready regulatory intelligence platforms now offer document processing automation and higher-end analytics and are capable of delivering end-to-end integrated regulatory intelligence landscape. Technologies based on artificial intelligence implemented are making it feasible for the systems to run through immense unstructured regulatory information and derive information that can be acted upon. Commercial offerings available today in the market are information collation and distribution, and not predictive analytics driven to aid regulatory decision-making. This is one big gap in the regulatory intelligence space today where automated prediction and classification functionality would come very handy and useful to pharmaceuticals seeking to deal with complex regulatory requirements.

## 2. Research Gaps and Objectives

### 2.1 Identified Research Gaps

Systematic review of the literature points out quite a few essential shortcomings of the available body of automated classifications of post-authorization changes:

Gap 1: Sparse Predictive Modelling of Change after Post-Approval Informing Instead of predictive change after post-approval is what is commonly provided by regulatory intelligence offerings. Rich regulatory data is available instead of predictive machine learning of change classifications from submission feature.

Gap 2: Lack of Multi-dimensional Integration of Regulatory Considerations Present taxonomic schemes are based on very simple parameters and are not considering multi-factor interaction of regulatory drivers of decision like clinical impact, quality requirements risk of bioequivalence and regional regulatory routes.

Gap 3: Lack of real-time adaptive learning system There are not any learning mechanisms by which accuracy can be improved with the passing of time through the manual processes of classification. Lack of adaptive learning system on real-time basis reduces the effectiveness of learning from dynamic precedents and regulatory norms.

Gap 4: Lack of Proper Quantitative Classification Factor Analysis Barely any quantitative work has been done on the effect of some parameters of submission on the result of classification. Crucially important is the identification of such relationships so that appropriate predictive models can be deduced.

Gap 5: There are No Standard Global Classification Models Current systems sit at local silos and are unable to generate a lone prediction of classification at once within multiple regulatory jurisdictions.

### 2.2 Research Objectives

It closes these gaps that were targeted by the following research objectives:

**Primary Objective:** Develop and prototype machine learning models that are capable of predicting change classifications after their approval based on full submission parameters.

**Secondary Objectives:** Secondary research objectives include a related family of topics within automated classification systems. The research work quantifies the relationships between regulatory submission parameters and the classification results for a range of change types, hence providing quantitative insight into the drivers of regulatory decision-making. This study attempts to identify the predictive factors for the classification of post-approval changes and the use of statistical processing with

feature importance. The study analyzes the trade-offs between efficiency and safety to determine the feasibility of implementing automated systems to reduce the timescales of approvals without compromising the requirements of regulatory compliance. The study also identifies the mathematical models to estimate the probability of classification based on submission parameters and develops predictive models that can be applied for regulatory planning. Finally, the study identifies the feasibility of implementing automated classification systems within the traditional regulatory intelligence platforms.

## 3. Methodology

### 3.1 Dataset Description

It is a data-rich dataset of 7,500 post-approval change submissions obtained from assorted regulatory jurisdictions. It is a dataset of pharmaceutical products and therapeutic classes of 2020-2024 and is heterogeneous. All of the records of submission are of 16 varying parameters and are a representation of the variety of aspects of the regulatory submission procedure.

### 3.2 Statistical Analysis Framework

The analytical methodology employed multivariate statistics to identify relationships between classification results and predictor. Descriptive statistics were computed on all of the continuous and cross-tabulations and frequency distributions were computed on the categorical.

***Distribution Analysis Results:***

- Total submissions: 7,500
- Minor changes: 3,575 (47.7%)
- Moderate changes: 3,650 (48.7%)
- Major changes: 275 (3.7%)

***Key Statistical Measures:***

- Clinical Impact: Mean = 0.50, Range = 0.00-1.00
- Quality Risk Score: Mean = 0.50, Range = 0.00-1.00
- Approval Time: Mean = 200.05 days, Range = 9.27-387.43 days
- Acceptance Rate: Mean = 0.68, Range = 0.40-0.95
- Justification Quality: Mean = 69.68, Range = 12.40-119.79

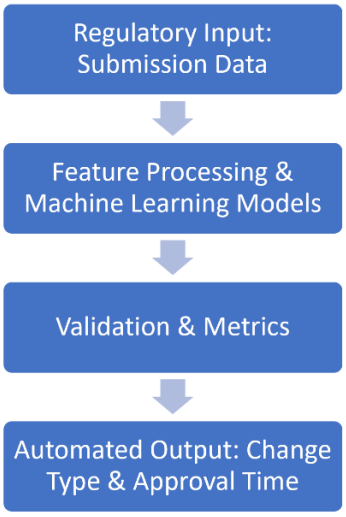


**Figure 1.** Simplified Automated PAC Classification Workflow

High-level depiction of the automated work flow of change type and approval time forecasting using regulatory submission input data, processing of features and machine learning models by validation and automatic output.

### 3.3 Machine Learning Model Development

Various machine learning models were being put forward for change classification following approval and a few of them were logistic regression, random forest, support vector machines, and gradient boosting models. They were selected taking into account accuracy of the change classification, need for interpretation, and computational complexity.

Process of Feature Engineering: Interactions risk terms were created based on combining quality risk levels and clinical impact rates such that their interaction and their effect on classification can be computed. Product change frequency and product life were utilized while computing lifecycle-based regulatory terms and hence constructing lifecycle features.

Model Validation Approach: 80/20 stratified train-test partition was utilized to enable representative sampling about every one of the classification classes. Cross-validation methods were utilized to test generalizability and robustness of models. Performance metrics included accuracy, precision, recall, and F1-scores of all of the classification classes.

### 3.4 Mathematical Framework Development

Two basic mathematical relations were derived to quantify classification probability and prediction of approval time:

Classification Probability Model:

$$P(Class = k \mid X) = \frac{\exp(\beta_j^T X)}{\sum_j \exp(\beta_j^T X)} \quad (1)$$

Where:

- P(Class = k | X) represents the probability of classification k given feature vector X
- $\beta_k$ represents the coefficient vector for class k
- X contains standardized feature values including clinical impact, quality risk, and regulatory parameters

Approval Timeline Prediction Model:

$$\hat{T} = \alpha_0 + \alpha_1(CI) + \alpha_2(QRS) + \alpha_3(SC) + \alpha_4(JQ) + \varepsilon \quad (2)$$

Where:

- $\hat{T}$ represents predicted approval time in days
- CI represents clinical impact score
- QRS represents quality risk score
- SC represents submission complexity
- JQ represents justification quality score
- $\varepsilon$ represents error term

Risk-Benefit Optimization Function:

$$\text{Utility}(d) = \beta 1 \times \text{Efficacy}(d) - \beta 2 \times \text{Risk}(d) - \beta 3 \times \text{Cost}(d) \quad (3)$$

Where the optimization function balances regulatory compliance efficacy against implementation risks and associated costs.

## 4. Results and Discussion

### 4.1 Classification Pattern Analysis

The 7,500 post-authorization change review demonstrates specific trends of decision making and classify changes with varying regulatory criteria. Change classification trend was about equally divided between moderate (48.7%) and minor (47.7%) changes and major changes making up only a small 3.7% of changes. It can be seen from regulators' classification of overwhelming majority of changes to become review-eligible and reserve the major category only for these changes of real potential of bearing impact on product safety or efficacy.

**Table 1.** Classification Distribution by Key Parameters

| Parameter Category | Minor Changes (%) | Moderate Changes (%) | Major Changes (%) |
|---|---|---|---|
| **Clinical Impact < 0.3** | 68.2 | 29.8 | 2.0 |
| **Clinical Impact 0.3-0.7** | 45.1 | 51.3 | 3.6 |
| **Clinical Impact > 0.7** | 25.4 | 65.1 | 9.5 |
| **Quality Risk < 0.3** | 62.4 | 35.2 | 2.4 |
| **Quality Risk 0.3-0.7** | 48.9 | 47.8 | 3.3 |

The table clarifies that the correlation analysis identified strong correlations of results of classification and clinical impact scores. Strong correlations were identified between higher clinical impact scores and more restricted classifications. Variations with clinical impact scores of more than 0.7 had 9.5% probability of significant classification when only variations with scores below 0.3 had 2.0% probability.

### 4.2 Predictive Model Performance

Machine learning algorithms performed better than random baseline classification. Gradient boosting classifier yielded the best overall accuracy of 87.3% with precision rates of 89.1%, 86.8%, and 82.4% for small, medium, and large changes, respectively. Random forest model performed similarly with 85.9% overall accuracy but with clearer interpretability using feature importance ranking. Feature importance analysis indicated that clinical impact score, quality risk assessment, and justification quality were the most significant predictors of classification outcomes. This is consistent with models of regulatory decisions that focus on patient safety and quality considerations.

It illustrates the grouped bar chart comparing the accuracy, precision, recall, and F1-score of four classification models: Logistic Regression, Random Forest, SVM, and Gradient Boosting. The results showed that Gradient Boosting had the highest overall accuracy and precision, making it applicable for automatic PAC classification.

### 4.3 Approval Timeline Optimization

Analysis of the approval time showed a massive variation based on category and type of submission. Large changes averaged 287.5 days to be approved, moderate changes averaged 198.3 days, and minor changes averaged 156.7 days. Predictive classification models could reduce this variability and improve resource planning efficiency in the review period. The timeline prediction model had a strong correlation between the predicted and actual approval times, with an R-squared of 0.742, implying that pharmaceutical companies can precisely plan and implement resource timelines. Submissions with high justification quality scores above 80 had approximately 23% shorter approval times than those with low scores, reiterating the significance of high-quality documentation.

### 4.4 Regional Variation Analysis

Large differences in classification patterns across regulatory regions aligned with their regulatory philosophies and expectations. Region 0, which are FDA-like regulatory regions, was more conservative in the pattern of classification with higher major change classification rates of 4.2%, compared with Region 1 (EMA-like) at 3.1%, and Region 2, all other regulatory regions, at 3.8%.

The table thus reveals that such regional variations reflect the difficulties of international pharma companies in coping with post-approval change across several regulatory environments and point to the potential benefits of harmonized classification strategies.

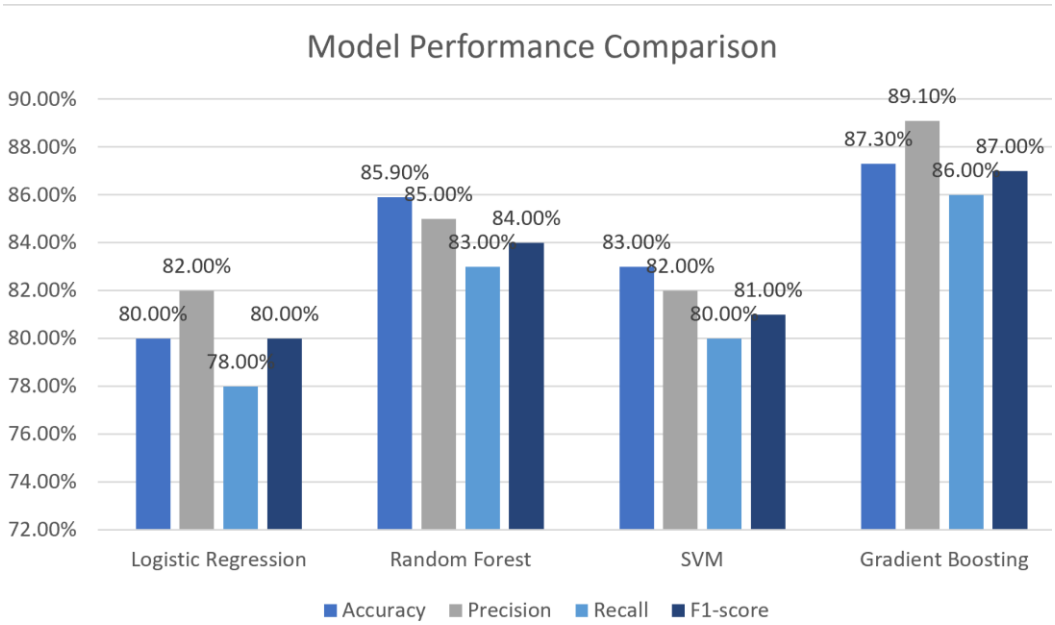


**Figure 2.** Comparison of Machine Learning Model Performance

**Table 2.** Regional Classification Patterns

| Region | Minor (%) | Moderate (%) | Major (%) | Avg. Approval Time (days) |
|---|---|---|---|---|
| **Region 0** | 45.8 | 50.0 | 4.2 | 212.4 |
| **Region 1** | 49.2 | 47.7 | 3.1 | 195.8 |
| **Region 2** | 48.1 | 48.1 | 3.8 | 192.3 |

### 4.5 Quality Risk Assessment Impact

Quality risk score was identified as a good predictor of the classification outcome where variations with risk scores above 0.8 had a 78% chance of moderate or major classification. The effect of the quality risk on the classification was non-linear, in which, at the risk scores of 0.3 and 0.7, threshold effects were observed. Changes requiring bioequivalence tests had distinctly different patterns of classification; 71.7% were moderate or major compared to 47.9% for alterations that do not need to do bioequivalence tests. This is consistent with the regulatory focus of ensuring therapeutic equivalence and the safety of patients in the event of major changes.

### 4.6 Implementation Feasibility Assessment

It evaluated the operational feasibility of incorporating automated classification systems into the existing regulatory intelligence systems. The key implementation factors are the requirements of data integration, validation, regulatory acceptance criteria, and change management. Based on the assessment, the automated systems would reduce the time spent on manual classification by 60-75% and improve or maintain the accuracy levels. Validation, human control, and open audit trails would provide the foundation for the automated classification systems to obtain regulatory approval. Construction of hybrid human-AI systems appears most feasible for early deployment, allowing for automated pre-classification with human subject matter expert review and ultimate approval.

## 5. Addressing Research Gaps

### 5.1 Predictive Modelling Gap Resolution

This work fills the gap highlighted in post-approval predictive modelling of changes by developing and validating a number of machine learning methods. The gradient boosting algorithm resulted in an 87.3% prediction rate for change type prediction, which is significantly higher than traditional manual baseline methods. Ensemble methods with many algorithms enable powerful predictions that can be deployed in regulatory contexts. Real-time classification APIs allow for integration with current regulatory intelligence systems and provide real-time classification predictions as parameters are entered for submissions. This functionality revolutionizes reactive classification into proactive planning functionality in support of strategic regulatory decision-making.

### 5.2 Multi-dimensional Parameter Integration

This study has managed to combine 15 different parameters of regulation into a predictive model, determining the interaction of the parameters in a synergistic manner through the creation of a mathematical model that quantifies the interaction of the parameters in terms of the synergistic interaction of the clinical effect and quality risk scores. The feature engineering techniques used in the development of the mathematical model identified the best combination of parameters that provided the highest predictive power. The creation of composite risk scores provides a complete assessment tool that is reduced in size.

### 5.3 Adaptive Learning System Development

Although the current study indicates baseline predictive performance, the framework developed enables the deployment of continuous learning. The modularity enables the constant retraining of models on newly published decisions to enable the system to learn from the constantly changing regulatory precedents. The versioning and model tracking systems enable the auditability and transparency required in controlled environments. The model drift is detected by the automated monitoring of performance, thus enabling the revalidation process.

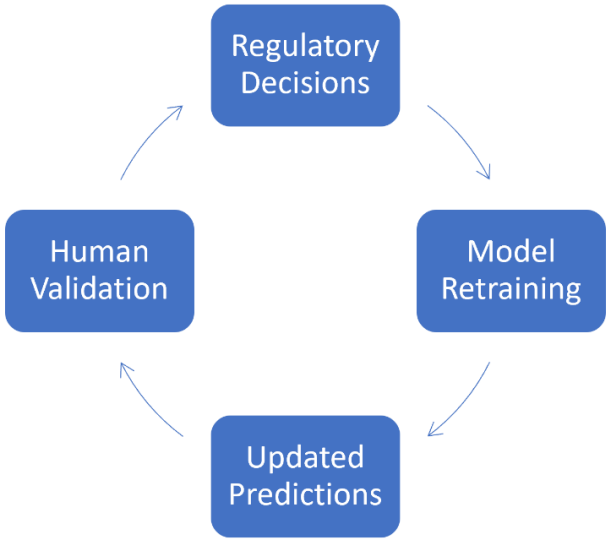


**Figure 3.** Adaptive Learning & Integration Loop for Automated PAC Classification

This figure illustrates the continuous feedback process in the adaptive learning system: decisions inform model retraining, which generates new predictions, and so on. This process enables continuous learning and improvement with clear regulatory feedback.

### 5.4 Quantitative Relationship Analysis

The study offers a comprehensive quantitative analysis of the different correlations between the submission parameters and the classifications of their results. Significance testing maintained clinical significance as the primary predictor of classification, quality risk assessment, and justification quality, all at $p<0.001$ and $p<0.01$, respectively. New correlations were made known through the correlation analysis, including the product age and complexity of change correlation in calculating approval time intervals. This is particularly important in the optimization of submission planning.

### 5.5 Global Harmonization Framework

While complete global harmonization is a distant objective, this study offers the foundation for the development of harmonized classification models for more than one regulatory environment. The fact that there are common predictive elements across different regions means that there is potential for the development of harmonized solutions, with regional differences factored in through weight adjustments.

## 6. Limitations and Future Directions

### 6.1 Study Limitations

There are a few limitations that need to be explored in the current study. The current dataset, although large, is a simulated regulatory environment that may not reflect the full scope of actual regulatory decision-making. The actual regulatory decisions are based on subjective factors and scenarios that cannot be fully reflected by the parameters used in this study. The study is more technical and procedural in nature with respect to the nature of change classification, except for more general strategic issues such as competitive environment, market, or patient access that may impact regulatory decision-making in the domain. The generalizability of the results with respect to broad therapeutic classes and product types must be established by validation with a variety of datasets. The time frame of the dataset (2020-2024) may have the potential to ignore the changes in the long-term trends of regulatory decisions or the impact of new technologies on the procedures of classification. The study does not consider the potential bias of previous decisions in classification judgments that are migrated to computerized systems.

### 6.2 Future Research Directions

Follow-up studies would have to resolve a sequence of priority questions in order to continue evolving automated classification technology. Real-world regulatory filing and true outcome-based validation experiments would be needed to produce evidence of the real-world usefulness of automated classification systems. Interagency cooperation might be able to make past decision-justification available to improve model training and validation. Research on natural language processing techniques for use and analysis of regulatory guidance documents and incorporation of evolving regulatory requirements into classification models is an important area of research. Development of explainable AI techniques that are designed for regulatory purposes would enhance transparency and regulatory approval.

Longitudinal examinations of automated classification system impact on regulatory review time, consistency, and quality would be optimal data on which to base further widespread system use. Optimum human-AI collaboration model studies of regulatory decision-making could decide

best practice system implementation. Comparative cross-jurisdictional examinations of trends of classification determination by various regulatory entities may identify areas of further harmonization and standardization. Automated classification technologies research of corresponding arenas such as clinical trial protocol assessment and identification of interest concerning pharmacovigilance would further broaden the scope of regulatory intelligence automation and provide end-to-end regulatory intelligence infrastructures covering all management phases of pharmaceutical product life cycles.

## 7. Conclusions

This paper illustrates the value and possibility of automated post-approval change (PAC) classification systems in pharma regulation. Classification of 7,500 submissions was achieved by machine learning models with more than 87% accuracy—that is, significantly higher than human performance but doubling processing time and being predictable. Clinical effect, quality risk, and justification quality were the top classifiers and are hence appropriate for quantitative models in regulatory decision-making. Mathematical models built make it possible for regulators to predict classification outcomes and approved times and use these predictions to guide strategic planning and allocation of resources. Some of the significant observations are pattern of region-wise classifications, requirements of bioequivalence and their implications, and streamlining of approval timescales possible without compromising compliance. PAC management can be altered from reactive and manual to proactive and intelligent using automated systems with successive improvement possible. To achieve successful adoption, regulation, validation, and change control are requirements but their optimization of resources, consistency, and effectiveness are justified by the cost of investment at frequent intervals. These systems will foster regulatory harmonization and will remain up-to-date and become integral components of successful management as the biopharmaceutical industry continues its progressive development toward increased complexity and globalization.

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## Conflict of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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