"Holistic Risk-based Site Surveillance – A Data-based Approach to Site Quality Risk Identification and Assessment in the Pharmaceutical Industry"

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Holistic Risk-Based Site Surveillance

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Abstract

Effective quality risk management is fundamental in guaranteeing the development and manufacture of high-quality drugs, reducing drug shortages, and avoiding harm to patients' health. The ability to accurately assess the actual risk environment, predict potential product quality or supply disruption issues and act to eliminate, prevent, reduce or mitigate them is key to improvements in quality management maturity. This paper illustrates a just-launched research project aimed at developing a comprehensive framework for how to assess and predict risks by leveraging a range of diverse factors.

Introduction

Risk management plays a crucial role in ensuring quality within pharmaceutical manufacturing. The U.S. Food and Drug Administration (FDA) recognises the importance of risk management to reduce rejected batches and drug shortages (FDA, 2021a). Initiatives in quality risk management at the plant level should holistically cover risks associated with all steps of the value chain and drug's lifecycle (ICH, 2005). However, it is still not uncommon to find risk analyses which focus on a single process or which are conducted with inputs from a single department or function and these efforts are not capable of comprehensively assessing the actual risk for a given pharmaceutical product. Regulatory initiatives, such as the Quality Metrics initiative, demonstrated that the assessment should consider all value-steps, numerous key performance indicators, the maturity of the sites as well as the respective context

(Friedli et al., 2019). FDA already prioritise their scheduled inspections based on a site risk assessment taking into consideration site type, time since last surveillance inspection, FDA compliance history, foreign regulatory inspection history, patient exposure, hazard signal, and inherent product risk (FDA, 2018). Earlier research has shown that the combination of compliance history data and additional parameters, such as operational and financial performance measures, helps to better predict future inspection outcomes (Eich & Friedli, 2021; Seiss, 2018). For this reason, the FDA is considering integrating additional indicators into their risked-based inspection scheduling algorithm (FDA, 2021b).

In addition, the recent COVID-19 pandemic has highlighted the urgent need to improve the capability of pharmaceutical industry regulators to remotely assess risk. With ongoing travel restrictions, the inspection process shifted from an on-site to a remote or hybrid approach, revealing new challenges and accelerating the necessity for a reliable risk assessment model. The University of St. Gallen, in collaboration with Columbia University and an experienced risk management consultant and researcher, has been awarded a research project by the FDA to develop a comprehensive model to assess and predict risk within pharmaceutical production sites. This paper explains the project's conceptual framework, the related dimensions, the research approach, and the project's goals.

Combining Internal and External Risk Perspectives – The Research Framework

The research project aims at improving the current understanding of the different factors and dimensions influencing pharmaceutical quality risk by performing qualitative and quantitative analyses. According to the technical proposal: "*The project aims to create a comprehensive Remote Site Risk Surveillance Model, using data from the four dimensions outcome metrics, quality management maturity, compliance history, external signals, and their respective context factors*" (Friedli et al., p. 4). St. Gallen's previous contributions to the quality metrics initiative (cf. Friedli et al., 2017, 2018, 2019) have shown that the effectiveness of a pharmaceutical quality system cannot be analysed based on isolated metrics but requires the consideration of different dimensions to depict the real situation. Similarly, the assessment of pharmaceutical product risk should be based on the combination of multiple dimensions coming from inside and outside the manufacturing site. The assessment of a Site Risk Surveillance Score must be based on specific site characteristics in conjunction with wider organizational factors to guarantee that the overall risk environment is analyzed correctly. The project's four dimensions as well as the background context factors are displayed in Figure 1 and described in more detail below.

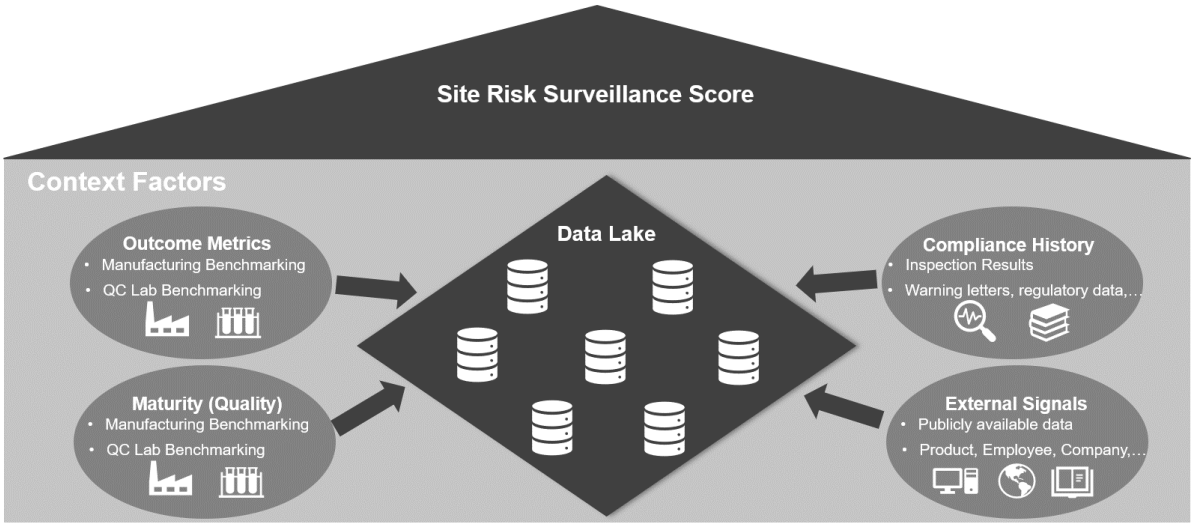

Figure 1: Conceptual Framework of the Site Risk Surveillance Score (T. Friedli et al., 2021)

The *Context Factors* define the boundaries (e.g. environment) where a site is located. These context factors provide the confinement in which the analyses are performed and will inform the weighting system for data aggregation and the site risk surveillance score calculation.

Manufacturing and quality performance metrics are an important source of information for risk management, especially at the site level. Early attempts to assess quality risk and predict future inspection outcomes have mainly focused at the pharmaceutical site level, without considering the external environment (Eich & Friedli, 2021; Friedli et al., 2019). The site's risk profile has been operationalised in two major dimensions: quality maturity and operational performance. These two dimensions are interrelated, since a higher adoption of best practices, i.e. higher maturity, leads to better operational performance (Voss et al., 1995). Building on that, the project team integrated these two dimensions, concentrating on depicting the actual situation within the site. On the one hand, manufacturing performance has been operationalized as *Outcome Metrics*. Operational information will be provided by the St. Gallen Operational Excellence (OPEX) and quality control (QC) laboratory databases. Metrics, stemming from these databases, will be identified that can predict underlying pharmaceutical quality risk in several dimensions such as Total Productive Maintenance, Total Quality Management, and Just in Time. On the other hand, the actual implementation level of operational practices will be assessed with the dimension termed *Maturity (Quality)*. Similar to the performance dimension, the maturity dimension relies on both the OPEX and QC lab databases. The St. Gallen OPEX database contains more than 180 survey items related to the implementation of OPEX practices in manufacturing, and the QC labs consist of about 70 practices related to the laboratory. Indicators found to have the strongest predictive power will feed into the final risk surveillance model of this project.

The Compliance History dimension will consider different types of compliance history data, for example, the factors listed in FD&C Act 510 (h)(4). This dimension also provides the historical regulatory data necessary to train the algorithm to predict inspection outcomes. Seiss (2018) demonstrated the power of compliance history to train predictive algorithms, particularly in combination with other data.

Pharmaceutical manufacturing facilities are not isolated entities, rather they are interconnected with the external environment. An externally originated risk might impact the internal production processes, and often the site has only limited possibilities or capabilities to manage these external risks. Nevertheless, the identification and assessment of external signals is a key element to prepare the plant, reduce the impact of externally generated events, and avoid a reactive fire-fighting approach. Therefore, this project will focus on identifying and assessing public information to improve the predictability of the model and provide a comprehensive picture that considers both the internal and external environment. The *External Signals* will be used to triangulate the information from the two internal dimensions (outcome performance and quality maturity), to inform the Site Risk Surveillance Score with external data informing the consequences of internal processes.

The Site Risk Surveillance Score – Predicting Inspection Outcomes

A comprehensive risk prediction must consider diverse information from different data sources. For the purpose of the design and development of the model, operational performance and maturity information are readily available within the St. Gallen OPEX and QC lab databases. Available Compliance history data will be added. External signals can be 'crawled' by screening publicly available data from the internet and looking for specific signals related to the companies, their manufacturing facilities or their products. In this research project, external signals data will be scraped using an ontology-based information extraction framework. This ontology framework organises the different associations between the information sources to generalise and structure the data most relevant for the risk factors.

The information from the different data sources will be stored in a central data lake, which has been shown to provide better opportunities and flexibility compared to classic databases (Khine & Zhao, 2018). Data lakes can store different data formats and facilitate the development of statistical models. Nevertheless, the project team must carefully tailor this data lake to its purpose, avoiding raising the complexity of the data lake and turning it into a data swamp. Careful definition of an ontological structure for each of the four dimensions and the background context factors will provide structure to the data lake and avoid data redundancy.

The *Site Risk Surveillance Score* will be the result of the integration and aggregation of the four dimensions. The prediction model will rely on the centrally stored data to calculate the risk score based on the relevant context factors.

The development methodology for the Site Risk Surveillance Score will firstly determine the context factors for the site and therefore extract the relevant information from the data lake. Successively, machine learning algorithms will match compliance history with the information extracted from the data lake to develop predictive models. The process aims at understanding the contributions of various risk factors to the final risk score without compromising the quality of the prediction. The final goal of this research is to identify and refine *the optimal set of risk factors* from the dimensions that must be integrated into the model to obtain a reliable pharmaceutical product risk prediction based on the defined context factors.

Outlook and Next Steps

The research project aims at improving the understanding of pharmaceutical quality risk prediction in the pharmaceutical industry. The integration of internal and external factors is a new approach that has not been addressed before in either the literature or in practice. This innovative approach will provide several benefits to current pharmaceutical quality risk discussions: firstly, expanding the understanding of the impact of context factors in risk prediction, and secondly, by screening and assessing external data sources and defining an appropriate hierarchical ontology structure. Finally, developing a comprehensive predictive model that integrates several dimensions to provide a practical ready to use tool for the industry based on best available academic research.

The development of flexible predictive pharmaceutical product risks models capable of being adapted to different situations will provide numerous benefits to the industry. On the one hand, regulators will benefit from a more robust risk assessment methodology based on the current situation and its possible development. The risk assessment can inform the risk-based inspection scheduling process and prioritise situations that present the greatest potential harm to the patients. On the other hand, the model will contribute to improving companies' understanding of their risks, providing a holistic approach and not relying on analysis based on isolated dimensions, processes or departments. This will better inform management decisions and reduce reactive fire-fighting actions.

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