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Occupational Health Risk Management in Tablet Manufacturing: A Case Study of Non-Beta Lactam and Penicillin Production Units

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ABSTRACT: Background: In the pharmaceutical tablet manufacturing industry, health risks involve high occupational health risks, especially in handling active pharmaceutical ingredients (APIs). This research addresses the challenge that effective risk management is essential to safeguard worker health, particularly in the production of critical products such as Non-Beta Lactams (NBL) and Penicillin. Objective: evaluating and investigating occupational health risks in the NBL and Penicillin production units, identifying key risk factors and proposing strategies to reduce exposure. Methods: This study used an observational cross-sectional design was used, focusing on environmental conditions, particulate concentrations, and compliance with personal protective equipment (PPE). The framework based on the concept of Hazard Identification and Risk Assessment (HIRA) assessed the level of risk across all stages of production, including weighing, mixing, granulation, and coating. Findings: Unit NBL indicated higher particulate levels (140 µg/m³) compared to unit Penicillin (100 µg/m³), especially during high exposure stages such as granulation, exceeding the WHO guideline (PM2.5 exposure is 25 µg/m³ for a 24-hour period) . The compliance with PPE was found to be lower in the NBL unit, which correlated with an increased incident rate. The risk assessment identified weighing and granulation as high-risk stages, requiring stricter controls. Conclusions: Reducing occupational health risks in the NBL and Penicillin units urgently requires improved engineering controls, PPE protocols and worker training. Model limitations highlight the need for enhanced risk assessment tools to improve safety outcomes.

KEYWORDS: Occupational health; risk management; tablet manufacturing; non-beta lactam; penicillin.

1. Introduction

The magnitude of potential risks associated with handling active pharmaceutical ingredients (APIs) makes occupational health a critical concern in the pharmaceutical industry, especially in tablet manufacturing [1]. A study found contamination in 68.3% of samples collected from pharmaceutical industry environments, with environmental monitoring results ranging from 0 to 15,000 ng/cm² [2]. However, occupational health is not only about ensuring the safety and well-being of workers but also about maintaining product quality and compliance with regulatory standards. This is particularly important in specialized areas such as non-beta-lactam (NBL) and penicillin production, where exposure to APIs poses significant health risks. Pharmaceutical production environments present a variety of occupational hazards, ranging from chemical exposure to physical risks [3]. Workers exposed to APIs face serious health risks, including potential carcinogenic, mutagenic, and toxic effects on the reproductive system [2, 4]. Studies have shown that chronic morbidity patterns among exposed workers include a higher prevalence of heart diseases, respiratory diseases, and chronic bronchitis compared to non-exposed workers [5]. Both inhalation and dermal exposure serve as significant pathways for API uptake, with dermal exposure being the primary route for certain potent compounds such as fentanyl [6]. Therefore, the ultimate goal of occupational health in the pharmaceutical industry is to mitigate these risks, ensuring worker safety and preventing contamination of manufactured products.

In addition, APIs are often designed as highly potent substances, meaning that even low-dose exposure can have biological effects [7, 8]. Workers handling these compounds risk exposure through inhalation, skin contact, or accidental ingestion. Prolonged exposure can result in serious health issues such as respiratory distress, skin sensitization, or systemic toxicity. Furthermore, product integrity is another crucial reason for prioritizing occupational health in pharmaceutical manufacturing [9, 10]. Cross-contamination between products can occur if containment and hygiene protocols are not strictly followed, especially in multi-product facilities. Preventing such contamination is essential for maintaining the safety and purity of the final product [11, 12]. Therefore, regulatory compliance is necessary to protect both workers and the company. Pharmaceutical companies must adhere to strict regulations set by organizations such as the Occupational Safety and Health Administration (OSHA) to avoid penalties and product recalls [8, 13–15]. Compliance with these standards ensures a safe working environment and legal adherence.

2. Materials and Methods

2.1. Study design.

This study employed an observational cross-sectional design to assess occupational health risks in tablet manufacturing, specifically in Non-Beta Lactam (NBL) and Penicillin production units. The primary objective was to evaluate environmental risk factors associated with each stage of the tablet manufacturing process and to identify areas for potential improvement in occupational health risk management. No demographic or individual characteristics of employees were collected, as the focus remained solely on process-related risks.

2.2. Data collection.

Data collection for this study was conducted in a pharmaceutical industry in East Java, Indonesia, within the NBL and Penicillin units, following a structured observation protocol designed to obtain information on environmental conditions, risk assessment documentation, and incident and hazard reports. The data collection was integrated into In-Process Control (IPC) procedures during the production process, which are standard in pharmaceutical manufacturing. Measurements of temperature, humidity, and particulate matter concentration were recorded at key stages in the production process (e.g., weighing, mixing, granulation, coating). These measurements were taken to identify variations in environmental risk factors that may affect occupational health risks. Additionally, reports of existing risk assessments were reviewed to establish baseline data on the hazards identified in the facility. These documents provided insight into known occupational health risks and the effectiveness of current control measures in mitigating those risks. Moreover, incident records and hazard reports were assessed to determine trends in occupational health incidents, such as respiratory problems or skin irritation, that may have been related to exposure to process-specific hazards.

2.3. Occupational health risk assessment.

The Hazard Identification and Risk Assessment (HIRA) framework was used as the risk assessment concept in this study. The framework enabled the systematic identification of occupational hazards at each stage of the production process. The risk level for each identified hazard was assigned based on the severity of the potential health outcome and the likelihood of occurrence. The probability of health impact due to exposure was rated as low, medium, or high. The ratings within this framework were categorized with specific implications for health effects, such as low exposure, which implied minimal exposure unlikely to cause significant health effects. Medium exposure implied a moderate likelihood of causing reversible health effects, and high exposure indicated frequent or severe exposure with a high probability of irreversible health impacts [16–18]. In addition, the occurrence of exposure was assessed based on historical incident data and environmental measurements. The hazards were subsequently prioritized based on their combined risk score, enabling the identification of high-risk stages that required further control measures.

2.4. Data analysis.

The data were analyzed using descriptive statistics in Python to summarize environmental measurements and the frequency of occurrences. A comparative analysis of particulate matter concentration levels between the NBL and Penicillin units was conducted to determine significant differences in exposure levels. The risk scores for each production stage were also analyzed to prioritize high-risk processes.

3. Results and Discussion

3.1. Environmental conditions and particulate concentration levels.

Table 1 summarizes the environmental conditions in the Non-Beta Lactam (NBL) and Penicillin units. Both units maintained an average temperature of 22.5°C and 50% humidity,

which are essential parameters for preserving pharmaceutical quality. According to observation notes, during granulation, high-strength pollutants, including particulate matter, were emitted. However, a notable difference was observed in particulate concentration, with the NBL unit averaging 140 μg/m³, compared to 100 μg/m³ in the Penicillin unit. Effective ventilation strategies are crucial to mitigate these emissions and protect worker health [19].

Table 1. Overview of the environmental conditions and particulate concentrations.

Unit	Temperature (°C)	Humidity (%)	Average Particulate Concentration (μg/m³)
Non-Beta Lactam	22.5	50.0	140
Penicillin	22.5	50.0	100

Meanwhile, the illustration of our findings in Figure 1 describes these differences. We highlight the particulate exposure in the NBL unit, which presents a relatively higher environmental risk, particularly during stages that generate dust particles, such as granulation and weighing.

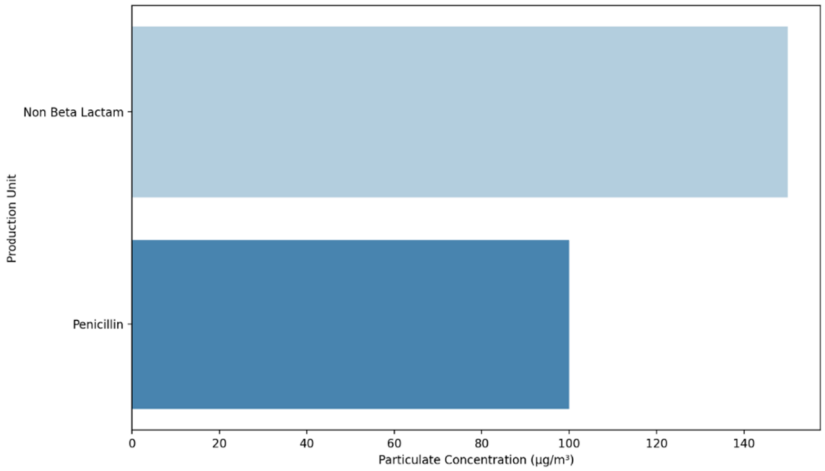

Figure 1. Comparison of particulate concentration levels.

The elevated particulate concentration in the NBL unit may be attributed to specific processes involving powdered materials, which are prone to becoming airborne. This increased exposure risk underscores the need for enhanced dust control measures, such as high-efficiency particulate air (HEPA) filters, to maintain safe air quality. In comparison, the Penicillin unit's lower particulate concentration might result from stricter containment protocols necessitated by penicillin's allergenic properties. Implementing similar protocols in the NBL unit could reduce exposure risk, especially during high-risk production stages. A study on environmental monitoring (EM) in pharmaceutical manufacturing highlights the importance of tracking particulate levels and microbial contamination to ensure a controlled environment for drug production [20]. This study emphasizes the need for continuous monitoring of non-viable particles, similar to the particulate concentration levels observed in our NBL and Penicillin units. The elevated particulate concentration in the NBL unit (140 μg/m³), compared to the penicillin unit (100 μg/m³), could be a result of less stringent containment protocols, as noted in our findings. In contrast, the Penicillin unit's lower particulate concentration might be due to stricter containment measures, which are essential for handling allergenic substances like penicillin.

3.2. Risk Score distribution by production stage.

Table 2 provides a breakdown of risk scores by production stage for both units, categorized as high, moderate, or low. The weighing and granulation stages were identified as high-risk in the NBL unit, with a risk score of 4, while the Penicillin unit exhibited a lower risk score of 2 for these stages. Coating was deemed low risk in both units, with minimal exposure to airborne particles. Figure 2 shows a density plot of these risk scores, indicating a concentration of high-risk stages within the NBL unit, primarily due to the absence of allergenic containment that is essential in Penicillin production.

Table 2. Risk scores for the specified production stages.

Production Stage	NBL Risk Score	Penicillin Risk Score	Risk Level
Weighing	4	2	High
Blending	2	1	Moderate
Granulation	4	2	High
Coating	1	2	Low

Another relevant comparison can be made with studies on the Quality by Design (QbD) approach, which focuses on identifying and controlling risks throughout the pharmaceutical development process [21]. The QbD framework emphasizes proactive risk management strategies to ensure product quality and regulatory compliance. In our study, risk scores were assigned to various production stages, with higher scores observed during weighing and granulation in the NBL unit. This mirrors the QbD principle of identifying critical process parameters that influence product quality and safety.

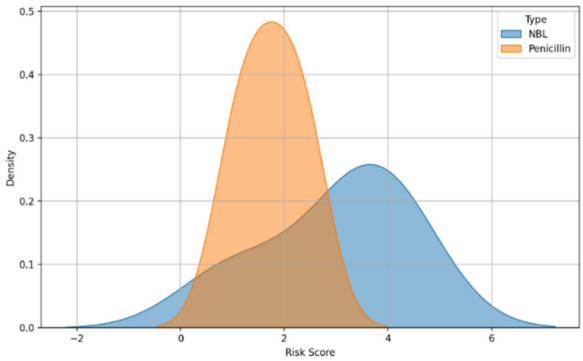

Figure 2. Density plot of risk scores for Non-Beta Lactam (NBL) and penicillin across production stages.

The findings in Table 2 and Figure 2 suggest that inadequate PPE compliance in the NBL unit may have contributed to a higher frequency of incidents, as PPE serves as a critical barrier against API exposure. In contrast, the Penicillin unit demonstrated higher compliance, reflecting stronger adherence to protective protocols, likely due to heightened awareness of penicillin allergies. Reinforcing PPE protocols through regular audits and worker training, particularly for tasks with high exposure potential, could help reduce incident rates in the NBL unit. Additionally, mandatory PPE compliance checks should be introduced to enhance worker protection across both units. The importance of corrective and preventive actions (CAPA) has also been highlighted in studies exploring quality assurance methods within pharmaceutical manufacturing [22]. CAPA frameworks are designed to detect, address, and prevent quality issues through structured problem-solving approaches. In our study, we

recommend reinforcing PPE protocols and introducing compliance checks to mitigate risks in the NBL unit. This recommendation aligns with CAPA principles, where root cause analysis would identify inadequate PPE compliance as a contributing factor to higher incident rates during high-risk production stages.

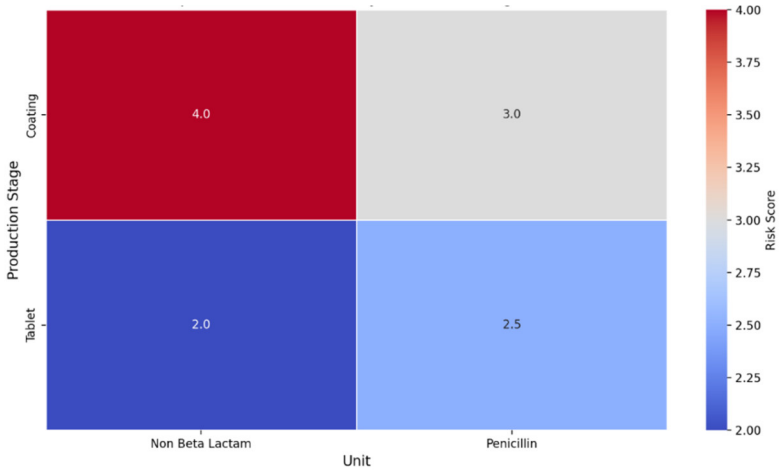

Figure 3. Risk assessment mapping by production stage and unit.

The high-risk scores for weighing and granulation processes in the NBL unit indicate increased exposure to airborne particulates and API contact during these stages. In contrast, the lower risk in the Penicillin unit can be attributed to stringent containment measures that effectively limit dust and aerosol generation. Therefore, adopting similar measures in the NBL unit, such as isolators or enhanced ventilation, could help reduce exposure. Furthermore, this risk distribution underscores the need to prioritize engineering controls and PPE in high-risk NBL stages to minimize potential health hazards.

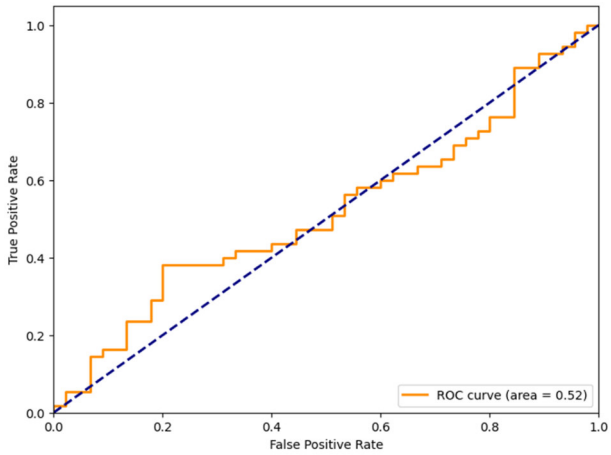

Figure 4. ROC curve for high or low risk clasification.

The ROC curve in Figure 4 illustrates the model's ability to distinguish between high- and low-risk classifications. The area under the curve (AUC) quantifies this capability, with a value close to 1 indicating excellent discrimination. In the context of Occupational Health Risk Management, this suggests that the model can reliably identify higher-risk production units, enabling targeted interventions to enhance worker safety. However, the AUC value of 0.52 indicates that the model performs only slightly better than random chance in distinguishing between the two classes. In practical terms, this suggests that the model is not

particularly effective at classifying risks, as an AUC of 0.5 would indicate no discrimination ability at all. For comparison, a study on predicting long-term sickness absence (LTSA) using occupational health survey variables achieved an AUC of 0.68, indicating moderate discrimination between employees at risk of LTSA and those not at risk. The dashed line in the ROC curve represents the baseline performance of a random classifier, serving as a reference point [22]. The closer the ROC curve is to the top left corner of the plot, the better the model's performance. This insight is crucial for Occupational Health Risk Management, as it highlights the need for further model refinement to improve predictive accuracy. In studies involving deep learning models for predicting Type 2 Diabetes (T2D), such as those using autoencoders or deep neural networks, AUC values exceeding 0.80 were reported [19, 21]. These models demonstrated strong discriminatory power by capturing complex relationships within large datasets. Although these models belong to a different domain (healthcare), they underscore how advanced machine learning techniques can significantly improve predictive accuracy. This comparison suggests that exploring more sophisticated modeling approaches, such as deep learning, could enhance our risk classification model's performance.

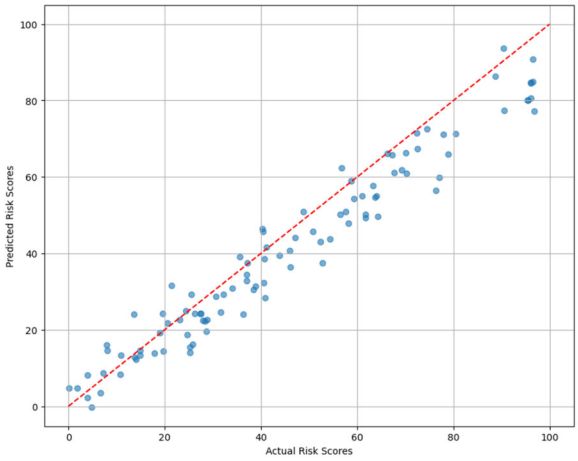

Figure 5 Correlation between actual and predicted risk scores.

The scatter plot in Figure 5 illustrates the relationship between the actual and predicted risk scores generated by the model. The high correlation between these scores suggests that the model effectively captures risk patterns. Furthermore, the closer the points are to the red dashed line (which represents perfect predictions), the more accurately the model reflects real-world risk assessments. This correlation is crucial in Occupational Health Risk Management, as it enables the identification of potential hazards and the implementation of appropriate safety measures. For instance, if the model predicts a high risk for a particular activity, it can prompt further investigation and the establishment of control measures to reduce exposure. Importance values obtained from the model indicate which features contribute most significantly to the predictions. Features such as "Activity," "Existing Controls," and "Potential Risk" may have higher importance values, highlighting their key role in determining risk levels. By understanding these values, risk managers can prioritize the most impactful factors, ensuring that resources are allocated effectively to mitigate risks. In tablet manufacturing, this could involve enhancing training for high-risk activities or improving existing controls to address identified hazards.

Occupational health is also a critical component of environmental safety [20]. Pharmaceutical companies must ensure that hazardous materials are properly handled and disposed of to prevent contamination. Safe waste management is essential for sustainability and public health [21]. In NBL production, airborne exposure poses a significant risk, as APIs are often processed into fine powders. These particulates can become airborne, leading to respiratory problems or systemic effects. Additionally, dermal exposure, where APIs are absorbed through the skin, can cause allergic reactions or sensitization. Chronic exposure to particulates presents significant health risks, including respiratory and cardiovascular diseases. Long-term exposure has been strongly associated with conditions such as occupational asthma and chronic obstructive pulmonary disease (COPD) [19]. For example, workers exposed to herbal dust have shown reduced lung function and increased work-related symptoms [20]. Moreover, particulate exposure has been linked to cardiovascular effects, such as hypertension, myocardial infarction, and cardiac arrhythmias [21]. These risks pose serious challenges for the pharmaceutical industry, potentially leading to increased absenteeism, reduced productivity, and legal liabilities. Therefore, implementing effective control measures, adhering to Occupational Exposure Limits (OELs), and conducting regular monitoring are essential strategies for mitigating risks and protecting worker health.

Penicillin production presents additional risks due to its allergenic potential. Workers exposed to penicillin dust or vapors may experience severe allergic reactions, including asthma. To prevent cross-contamination, strict containment protocols must be enforced, including specialized equipment and PPE. In both NBL and penicillin manufacturing, mitigation strategies are essential to ensure worker safety. Workers should use PPE, such as respirators and gloves, to minimize exposure to hazardous APIs [22]. Additionally, engineering controls, such as isolators and HEPA filters, along with regular training and waste management protocols, play a crucial role in protecting both workers and the environment. This study's focus on a single-site facility limits its generalizability. Future research should involve multi-site studies to validate findings across diverse manufacturing settings. Furthermore, the lack of long-term exposure data prevents an assessment of chronic health effects, which should be explored in longitudinal studies.

4. Conclusions

This study highlights the critical yet under-researched occupational health risks in the pharmaceutical industry, specifically in tablet manufacturing within NBL and Penicillin production units. It underscores the need for effective risk management measures to mitigate exposure risks, particularly the high particulate levels and elevated risk scores observed at certain production stages. Additionally, fostering a stronger safety culture is essential, with an emphasis on engineering controls, improved PPE protocols, and regular training to reduce exposure. This research also provides initial insights into a risk assessment model, which, despite its limited predictive accuracy, demonstrates the need for further refinements to enhance risk identification and prioritization. Strengthening health and safety practices within the pharmaceutical industry can significantly improve worker protection, reduce incident rates, and ensure regulatory compliance.

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Author Contribution

Conceptualization: Arie Arizandi Kurnianto; Methodology: Reski Syamsu; Data Collection and Analysis: Reski Syamsu, Arie Arizandi Kurnianto; Writing and Review: Reski Syamsu, Arie Arizandi Kurnianto, Josfirin Uding Rangga; Supervision: Arie Arizandi Kurnianto, Peter Thokozani Phiri.

Competing Interest

All authors declare no competing interest from any other party influence this research.

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