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Human Factors Analysis and Classification System Interrater Reliability for Biopharmaceutical Manufacturing Investigations

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Abstract

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by

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Post Master Certificate Biotechnology Management, Penn State University, 2005

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Management

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Abstract

Human errors are an expected result of operations performed by individuals and frequently lead to accidents and other catastrophic events. The problem is that the current process used to investigate and mitigate human errors in the biopharmaceutical manufacturing industries is not effective, as it does not include the effects of human factors found to be effective in aviation and nuclear power organizations. The human factors and classification system (HFACS) was created for the investigations of accidents using the Swiss cheese model of accident causation as a theoretical framework. The purpose of this quantitative, inter-rater reliability study was to demonstrate the utility of the HFACS for human error investigations in the biopharmaceutical industry. The research questions focused on the level of agreement between independent raters using HFACS, as well as the difference in the level of agreement across different areas of biopharmaceutical manufacturing processes. In a fully crossed design, raters evaluated a stratified sample of 161 incident records further analyzed using Cohen's kappa, percentage agreement, and a 1-way analysis of variance test with Scheffe post hoc tests. Study results indicated the reliability of the modified HFACS taxonomy, which included no statistical difference ($p < .05$) with substantial Cohen's kappa values of .66. The social benefit of this study may stem from biopharmaceutical manufacturers using these findings to decrease human errors, improve the safety and reliability of their processes, decrease manufacturing costs, and support the development of drugs to address the unmet medical needs of society.

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Dedication

I dedicate this work to my family. To my wife Candy for keeping me company during this long journey and helping me maintain my focus. To my parents Roberto and Elba for the innumerable hours they spent praying to ensure that I had God as my guide and companion while I wrote. To my sister Sahilly and my brother-in-law Edgar for keeping me in good health. Finally, to my children Gabo, Lola, and Kiki, who endured the high and lows of my temper and the special vacations with my computer and me. Every one of them allowed me to realize that nothing is impossible if I put my best effort on the ones close to me and have faith that God is always with me.

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I have a special place in my heart for my committee chair Dr. Walter McCollum. I believe that he knows me better than I know myself. Thanks to Dr. McCollum I am a better person today. His dedication to his students has no limits, and his scholars (cohort) community is a testament of passion and vocation.

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Finally, I need to thank to all my coworkers. They endured my long conversations of frustration for many years. My two supervisors during the time I wrote my dissertation provided unlimited support and always made me feel that what I was doing is important. My associates were there every day, ensuring that I had the time I needed to complete my studies with words of encouragement.

Thanks to all, it meant a lot!

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Chapter 1: Introduction to the Study

Human errors are an expectation in operations performed by individuals. The general perception is that people are erratic and unreliable; therefore, they are the considered as the primary cause of errors and accidents (Dekker, 2006). Critical or complex processes that involve humans require special attention to prevent errors that will lead to accidents, and neglecting the vulnerability created by humans in execution may lead to catastrophic results.

Historically, catastrophic events in the aviation and nuclear power fields stimulated substantial research to control human errors. Accordingly, various models for accident investigations provide a framework for human investigation techniques (Berry, Stringfellow, & Shappell, 2010). With the aid of human investigation frameworks, practitioners have been able to improve the effectiveness of error investigations. The immediate result of improved investigational analysis leads to improved operations.

The aviation and nuclear power plant industries have experienced a reduction in accidents caused by human errors because of the implementation of the findings from the investigative tools and techniques developed to identify the causal factors. Studies conducted in the aviation and nuclear power industries have had a significant improvement in safety through the reduction of human errors in their operations (Liu, Nickens, Leon, & Boquet, 2013; Shappell et al., 2007; Vaughuen & Muschara, 2011). Based on past investigations into aviation and nuclear power accidents, the general perception of individuals as the primary cause for human error is misleading. Experts must consider many elements when evaluating the occurrence of human error, as front-

line operators are only part of the whole operating system. Human error investigation models indicate that errors are not random occurrences but rather the result of systemic, connected factors.

Leaders of organizations outside the aviation and nuclear power industries have applied human error models to investigate accidents. Researchers have conducted studies to mitigate the catastrophic results of accidents in maritime, railroad, and mining organizations, but those studies remain limited, as researchers have not investigated the areas of error-contributing factors in detail (Berry et al., 2010). A gap exists in determining the preempting and causal factors of human errors in executing a sequence of activities. Health care also has a gap in human error investigations, which represents a risk to individuals.

In the field of health care, for instance, although the catastrophic outcomes of accidents and errors are not as obvious as are those of a plane crash, they do represent a significant predicament for society. According to researchers at the U.S. Department of Health and Human Services (2013), unintentional accidents in operations pertinent to health care settings in 2010 represented the fifth leading cause of death in the United States. Accordingly, some researchers have shown that the human error models used in aviation and nuclear power organizations may be appropriate in health care (ElBardissi, Wiegmann, Dearani, Daly, & Sundt, 2007). The same models also apply to organizations in other industries susceptible to errors, including health care and particularly medicine production.

Biopharmaceutical manufacturing processes have complex operations, and although errors are not as disastrous, they represent a considerable burden to health care. Human errors have caused significant deviations, resulting in product quality issues as well as costly process interruptions (Clarke, 2009). Such process disruptions have delayed the entry of new drugs into the market, increased the cost of drugs, and contributed to the lack of product availability and affordability to the public. Although rare, some drugs incorrectly prepared or developed have led to fatalities. Therefore, the biopharmaceutical industry should benefit from better investigative tools to reduce and prevent these errors.

In this study, I evaluated the use of the human factors analysis and classification system (HFACS) taxonomy to assess how it may affect the current understanding of human errors in biopharmaceutical manufacturing operations and used the data obtained to explain how to implement human factor tools in these investigations. A reduction in human error in biopharmaceutical operations may improve reliability while minimizing the associated adverse effects. The elements of the study, the background, problem statement, purpose, nature, research questions and hypotheses, theoretical framework, significance, definitions of terms, assumptions and limitations, and concluding summary are in Chapter 1.

Background of the Study

Human errors are some of the most frequently identified causes of accidents by investigators. For example, accident investigators have counted human errors as the root cause of 70% of most aviation accidents (Liu et al., 2013; Wiegmann & Shappell, 2003).

Similarly, leaders in multiple industries attribute human errors as the main cause of accidents and production losses (Celik & Cebi, 2009; Vaughuen & Muschara, 2011; Wachter & Yorio, 2013). To address these issues, the authors of many studies in the literature of human error have attempted to identify methods to pinpoint the root cause of such human errors that are more efficient. Researchers studied how to identify the precursors of errors considering the elements around human factors, organizational and system-related failures (Wachter & Yorio, 2013). Researchers also examined human performance elements that could pinpoint active errors as well as error precursors (Wachter & Yorio, 2013). Although human factor models were originally for the aviation industry, the biopharmaceutical manufacturing field can benefit from such systems as well.

The manufacturing processes for pharmaceutical products, either typical methodologies or complicated processes such as biotechnology, are also vulnerable to human errors. As a result, experts at the U.S. Food and Drug Administration (FDA, 2003) recognized human errors as outcomes manufacturers should prevent. Additionally, product evaluators at the FDA recognized that human errors are more impactful to public safety than product defects (FDA, 2011). Although the costs associated with manufacturing these products are high, manufacturers cannot overlook quality.

All production costs, including losses, have a direct impact on the quality and effectiveness of the production activities, and leaders in manufacturing industries frequently try to control the overall costs of their operations. According to Clarke (2009), the losses attributed to human errors, particularly in the pharmaceutical industry, cost

billions of dollars every year. Human errors also have a negative impact on access to medicines in countries in which affordability is a challenge. Therefore, human errors represent an important component of the increased production costs due to product, materials, and time-associated waste.

However, the leaders of many companies attribute lack of training to be a main cause for human error and drive corrective and preventative actions toward that area. The corrective actions to address such human errors mainly relate to retraining labor not human factors (Poska, 2010). As a result, members of the manufacturing industry are unable to determine the true root cause of human errors (Clarke, 2009; Poska, 2010). Because of the significant effect of human errors on the manufacturing industry, it was imperative to study what contributes to causing them.

Although researchers have focused on this issue, they have recognized human performance is the way company leaders organize working operations. According to Wiegmann and Shappell (2003), multiple layers of an organization can lead to human errors. Such organizational tiers can include errors caused by structures other than workers, and latent causes include leadership and even organizational or functional structures (Wiegmann & Shappell, 2003), which leads to the notion that the cause of most human errors is a sequence of events rather than a single cause. The majority of incidents are the direct result of humans performing the function, and the remainder may be the result of a combination of further conditions of leadership but also specific conditions directly attributed to supervisors' organization of activities or even higher organizational demands indirectly affecting operators. Therefore, the best alternative to prevent workers

from making errors is to identify all the potential precursors and mitigate their effects on the operators.

In many instances, identifying and preventing errors is challenging, primarily because the problem is even more difficult to correct when people expect it, especially when humans conduct activities. A common perception is that errors are intrinsic to operations involving humans and therefore an expected outcome of the operations (Woods, Dekker, Cook, Johannesen, & Sarter, 2010). The study of human error from the perspective of learning from past issues is equally problematic due to the negative connotations associated with the performance of these types of studies. Although learning from mistakes seems to be wise, for some organizational leaders it is a difficult task because the origin of the knowledge is a negative event. Not all leaders in industries agree with this line of thinking.

Investigators in the aviation and nuclear power industries, for instance, have studied the human error phenomenon to decrease accidents and improve the safety of their operations. The studies of human error conducted by researchers for nuclear power and aviation organizations have reduced the adverse effect of such accidents (Stanton et al., 2013). Accordingly, accident investigators in the aviation industry have developed tools specifically for investigating accidents and incidents caused by human error. Investigators of the aviation and nuclear industries, driven by the urgency of the catastrophic results of accidents in their domain, have created models that study human elements beyond skills and training. In particular, accident investigators in the aviation industry developed HFACS to investigate the latent causes of accidents.

The HFACS is a hierarchical taxonomy developed to conduct causal factors analysis in aviation accidents. Wiegmann and Shappell (2003) developed the HFACS taxonomy to investigate military aviation accidents by subdividing causal factors into categories. The arrangement of the HFACS taxonomy of causal factors of errors into four hierarchical categories from bottom to higher order (organizational influences, unsafe supervision, and preconditions for unsafe acts and unsafe acts) is in Figure 1. Aviation accident investigators use the taxonomy to aid in analyzing accidents using the main causal factors in each category (Wiegmann & Shappell, 2003). The categories and codes of factors allowed the investigators to look for causes beyond the pilot or operators. The resulting investigations encompassed root cause detection at deeper levels and therefore more effective corrective interventions.

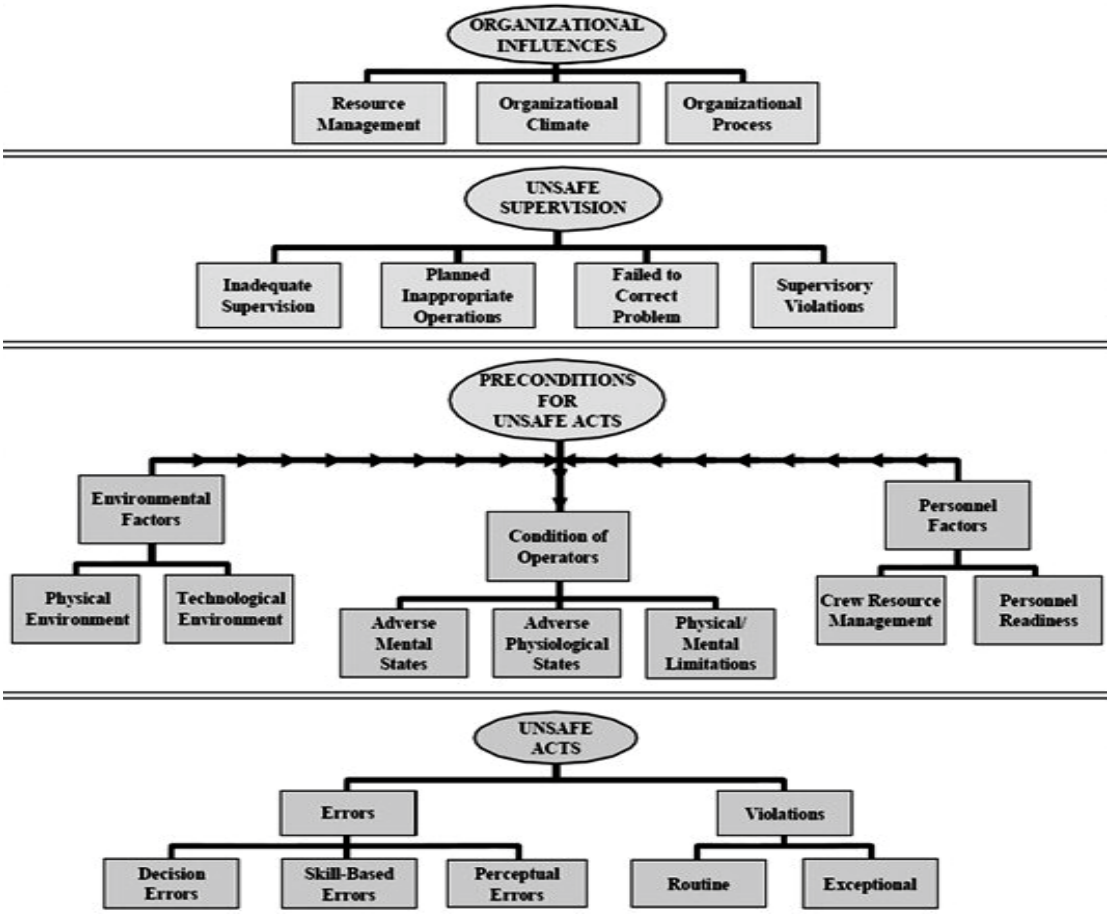

Figure 1. The HFACS. From *A Human Error Approach to Aviation Accident Analysis* (p. 71), by D. A. Wiegmann & S. A. Shappell, 2003, Burlington, VT: Ashgate. Copyright 2003 by Douglas A. Wiegmann and Scott A. Shappell. Adapted with permission.

The effectiveness of investigators using HFACS in aviation led to increased interest in other domains. Researchers demonstrated that investigators could effectively use HFACS in other industries to help in the investigations of accidents (Shappell et al., 2007). Accidents attributed to human error have been an area of concern globally, and HFACS has become a tool for reducing these issues. For instance, HFACS-derived methodology was suitable to analyze human error influences and to prevent these causes from recurring in merchant shipping accidents (Celik & Cebi, 2009; Xi, Chen, Fang, &

Hu, 2010). Furthermore, Celik and Cebi proposed modifications to the HFACS taxonomy that involved integrating a statistical model that provides a quantitative analysis of factors. The proposal for applying it to maritime accident investigations and enabling its quantitative elements was innovative. Although this was a significant step in maritime, as well as in other domains, the biopharmaceutical industry is different.

The use of human factors in pharmaceutical manufacturing organizations to investigate error is not widespread. Limited research exists on human error phenomena in pharmaceutical manufacturing organizations due to confidentiality concerns and a general unwillingness to share sensitive production information (Rodchua, 2009). In addition, the level of complexity and variety of pharmaceutical manufacturing processes make it difficult to assess human factor conditions during the operations. Another cause of this problem can be a lack of understanding by all levels of operations to appreciate the need to learn from previous mistakes to prevent recurrence. The negative implication of errors prevents organizational leaders from expanding the knowledge of such situations from an affirmative learning viewpoint (Edmonson, 2011). Further, the prevalence of human error may have been an expected development, as the leaders in the pharmaceutical industry did not face regulatory requirements to advance their understanding of the phenomena from the perspective of human factors until recently (FDA, 2011). The lack of regulatory oversight was only one reason for the stunted research attempts.

Another factor limiting research on error in the biopharmaceutical manufacturing is the lack of data available during investigations regarding the human factors conditions

of the events. As a result, complete databases with specific and detailed human error information are lacking the required details for pharmaceutical industries (Anand et al., 2006). The focus and interest of the leaders of each company are on generalizing during human error investigations (Anand et al., 2006). The available research is limited mainly due to the multitude of industrial applications as well as the proprietary concerns around the technological processes, which make it difficult to produce studies that yield the information required in the subject of human factors in error investigations. All these complications have prevented the development of human factors in error investigations in biopharmaceutical manufacturing.

Problem Statement

Human error is a routine part of life, and people will likely always be the cause of errors. The problem studied was that the current process used to investigate and mitigate human errors in the biopharmaceutical manufacturing industries is not effective, as it does not include the effects of human factors that have been effective in aviation and nuclear power organizations. The effect of human error is substantial; human error is a principal cause of accidents and has vast and potentially negative consequences in various industries, including aviation, nuclear power, transportation, and health care (Berry et al., 2010). Thus, organizational leaders devote a great deal of time and resources to reducing or preventing errors that may lead to the loss of resources, property, and even lives.

Companies involved in biopharmaceutical product manufacturing are subject to the adverse effect of human errors. For instance, FDA representatives established that

human error is a problem for drug manufacturing companies as well as for patients and users of their products, thereby serving as a risk to the public (FDA, 2003). The leaders of the organizations have the responsibility to protect the safety and efficacy of the products that the public receives (FDA, 2003). In addition, costs associated with human error in the biopharmaceutical industry include the health and quality of life of patients and increased cost and demand that negatively affect the health care cost burden carried by the population (Glavin, 2010). For these reasons, it is critical for researchers to pinpoint the causes of human error in the biopharmaceutical industry. Although researchers have not systematically investigated human error in biopharmaceutical engineering, industry leaders can benefit from research conducted in the field of aviation.

Researchers in the aviation industry have studied the phenomenon of human error in depth to reduce accidents and increase operational safety. Scholars have used the HFACS to investigate the causes of accidents (Shappell et al., 2007), thereby reducing accidents caused by human error. As a result of the HFACS, the rate of accidents has not increased since 2000, despite an exponential increase in the number of flights (Pasztor, 2012). Other researchers have shown the extended applicability of the HFACS to other types of industries for investigating accidents (Berry et al., 2010; Chauvin, Lardjane, Morel, Clostermann, & Langard, 2013; Shappell et al., 2007). My aim in undertaking this quantitative study was to evaluate the applicability of the classification segment of the HFACS to studying human error in the biopharmaceutical manufacturing industry and to determine how to reduce or eliminate the errors.

Purpose of the Study

The purpose of this quantitative study was to examine the utility of the HFACS to the investigation of human error and deviations in the biopharmaceutical industry to identify the factors that lead to human error in biopharmaceutical manufacturing operations. The results may help to improve organizational compliance with regulatory agencies by providing a more consistent system to determine the root causes of human error. Better root cause determination may result in more standard and effective corrective and preventive actions determination.

In this study, I used a taxonomy based on the attributes of the HFACS to evaluate data from process-deviation investigations in which the examiners considered human errors the root cause. I used the data to examine the reliability of the modified HFACS taxonomy in evaluating the causal attributes driving the occurrence of human error in biopharmaceutical manufacturing processes. Through the study, I provided information to assess the reliability of the modified HFACS taxonomy to investigate human errors in biopharmaceutical manufacturing operations. The variables measured in the study were the HFACS 18 human factors in the causal categories of task/act, preconditions, leadership/supervisor, and organizational influences. Specifically the variables measured were the following causal factors: resource management, organizational climate, organizational processes, inadequate supervision, planned activities, failed to correct the problem, rules and regulations violations, physical environment, technological environment, adverse mental state, psychological state, physical/mental limitations, teamwork, personal readiness, knowledge-based errors, skill-based errors, routine

violations, and exceptional violations. Further descriptions of the variables of the study are in Chapter 3.

Research Questions and Hypotheses

Substantial research in the literature extends the applicability of the HFACS to industries other than aviation for aiding in the investigation of accidents. Researchers have studied the utility of the HFACS in the maritime, mining, nursing, and surgery industries, among others (Shappell et al., 2007). In this study, I evaluated the extent of the reliability of the HFACS taxonomy to the investigation of human error in pharmaceutical manufacturing environments. The research questions were as follows:

RQ1: What is the level of agreement (Cohen's kappa) between the two independent raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes?

RQ2: What is the difference in the level of agreement (Cohen's kappa) across different areas (operational services, upstream manufacturing, and downstream manufacturing) between raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes?

The hypotheses for the research questions were as follows:

$H1_0$: The overall Cohen's kappa statistic between the two independent raters will not be substantial ($\kappa < .61$) based on the criteria set by Landis and Koch (1977).

$H1_a$: The overall Cohen's kappa statistic between the two independent raters will be substantial ($\kappa > .60$) based on the criteria set by Landis and Koch (1977).

$H2_0$: There are no significant differences between average Cohen's kappa statistics across the operational services, upstream manufacturing, and downstream manufacturing areas.

$H2_a$: There are significant differences between average Cohen's kappa statistics across the operational services, upstream manufacturing, and downstream manufacturing areas.

Theoretical Framework

The theoretical framework of the study was using the HFACS to determine and evaluate human error. The basis of the study of human error is human factor theory, which researchers developed within the nuclear industry and that allows for the evaluation of deviations and errors to make operations safer. Investigators in the aviation industry use human factor theory to evaluate their accidents (Reason, 1990). Human factor theories incorporate elements of organizational theories and their effects on examining the behaviors and actions causing human error. Investigators have incorporated those elements in various models in an approach to accident investigation.

Among the concepts developed for the approach to accident causation, or the Swiss cheese framework, was the idea that employees present the activities in productive systems in layers representing preconditions. In developing the Swiss cheese framework, Reason (1990) divided the actions that can cause an accident into active and latent conditions. Accidents occur when a layer breaks down or when systems have holes, thus causing degradations in the productive system. The Swiss cheese framework has since become a basis for other models and taxonomies.

The Swiss cheese framework is the basis of the HFACS. Reason's (1990) theory provided a definition for failures in productive systems. The HFACS further divided latent and active failures into causal factors, including categories and subcategories that examiners could use to determine the contributing factors in accident investigations (Wiegmann & Shappell, 2003). Examiners used the HFACS taxonomy effectively to investigate the causes of aviation accidents (Shappell et al., 2007). Researchers have since expanded this framework to other areas so they could use the model to investigate the associations between contributing factors and errors. Investigators may use those associations of contributing factors to determine the feasibility of the HFACS in investigating errors in other organizations.

In this study, I provided information regarding the utility of the HFACS theoretical concepts in the investigation of human error during the execution of production processes in manufacturing biopharmaceutical products. Through the HFACS, information regarding contributing factors in error investigations may be available, which may allow the treatment of error investigations from a higher causal perspective. I also examined the utility of the HFACS by determining how reliable and comprehensive the taxonomy is when used to investigate the causes of human error in different biopharmaceutical settings and to consider how they conform to the theories of human factors.

Nature of the Study

The focus of this quantitative study was to determine the utility of the HFACS for conducting human error investigations in biopharmaceutical manufacturing processes by

examining the validity of the taxonomy through its reliability. In this study, I modified the HFACS taxonomy to meet the needs of the biopharmaceutical manufacturing process. Through this quantitative interrater reliability study, I evaluated the validity of the modified HFACS for conducting investigations in the biopharmaceutical manufacturing process by examining the reliability of the taxonomy through determining the level of agreement among independent raters or interrater reliability.

The design was adequate for this study because the data provided information regarding the validity of the method to the extent that it produced the results expected. In this study, the measurement of the reliability among coders provided information regarding the utility of the HFACS for classifying human error in the biopharmaceutical manufacturing industry. The study included information regarding the degree of reliability on how different investigators can classify such errors from process deviation investigations of the biotechnology industry.

Studies in the literature include various approaches to examine the utility of human error taxonomies. For instance, Olsen (2013) showed how researchers conducted a variety of studies to demonstrate the reliability of the techniques used. The main factors considered in designing the reliability studies included the aim of the study, consideration and identification of factors, type of reports, and characteristics of the raters or coders (Olsen, 2013). To determine the methodology for the study, I considered similar factors based on the available literature.

In determining the methodology for the study, I considered and rejected several alternatives. For instance, the aim of the study was to determine the utility of an

established technique (HFACS) as well as the availability of investigation data. In this case, the data from the investigations were readily available, and the professionals in the field of biopharmaceutical incident investigations were homogeneous, as the level of training was similar. Therefore, there was no need to assess the reliability between various professions of participants as well as training level. The study involved assessing the level of agreement when participant investigators with the same level of HFACS training analyzed the same incident information independently.

The main measure of the validity of HFACS used in biopharmaceutical investigations was the level of agreement between raters. In this study, the analysis tool was Cohen's kappa. Cohen's kappa provides for a determination of agreement between raters, adjusting for agreement that will occur only by chance (Raheja & Gullo, 2012). Kappa is the most used tool for reliability in studies using the HFACS (Olsen, 2013; Wiegmann & Shappell, 2003). Although there is no difference between the particular characteristics of the reliability studies, the common factors are training, materials, and data to analyze. The majority of the studies establish a requirement of training hours for the raters that fluctuate from a few hours to up to 5 days, as well as data in the form of previous investigations (Olsen, 2013). The selected methodology for assessing the HFACS reliability included specific training, definitions of codes, and data from previous investigations. The methodology of reliability aligned with the most common studies presented in the literature.

Definition of Terms

The terms and definitions used in the study are as follows:

Action: The voluntary or deliberate performance of an act by a human at the interface between another human, system, machine, or environment (Hansen, 2006).

Biopharmaceuticals: Pharmaceutical drugs produced by using biotechnological recombinant manufacturing processes (Kayser & Warzecha, 2012).

Codes: Error factors presented in taxonomy for classifications. Investigators use the 18 factors in the HFACS as codes to determine the causal factors of investigations (Wiegmann & Shappell, 2003).

Error precursors: Preexisting conditions at a job area that increase the likelihood of human error during actions or operations (U.S. Department of Energy, 2008a).

Event: An incident caused by failures (Shappell et al., 2007). In the biopharmaceutical industry are classified as any non-conformance of processes and procedures.

Failures: Human, environmental, or equipment factors that cause a deviation from established procedures (Shappell et al., 2007).

Human error or failure: State or condition of being wrong in conduct or judgment and causing a failure in the actions to produce or achieve the expected result (U.S. Department of Energy, 2008a).

Human factors: Causal preconditions defining elements that can lead to human error (Shappell et al., 2007).

Human performance: A function of the balance between the capability of the individual carrying out the task and its demands (Whittingham, 2004).

Latent conditions: Deficiencies in management control processes or values that are not apparent but create workplace conditions promoting errors (U.S. Department of Energy, 2008a).

Near system event: Any unplanned, unforeseen occurrence that results from a failure of the system but that does not result in higher or catastrophic consequences (e.g., death, losses, or delays; U.S. Department of Energy, 2008b).

Overall Cohen's kappa statistic for interrater reliability: The average kappa statistic across all the individual kappa statistics derived from each of the individual factor ratings (Hanneman, Augustine, & Riddle, 2012).

Tasks: The mental, physical, or team activities required performing a procedure (U.S. Department of Energy, 2008b).

Validity: How well the HFACS measurements are in practicality when used for biopharmaceutical investigations. The focus of determining the validity of a framework was on the reliability of the users identifying causal factors (Wiegmann & Shappell, 2003).

Violation: Procedural or protocol deviation that is deliberate and not necessarily derived to generate an adverse effect. A violation could be a routine shortcut that can be unconscious or a break in the process with ignorance of its occurrence (Armitage, 2009).

Assumptions

I made various assumptions in this study and methodology. The first assumption was that I would have access to confidential data from the human error investigations of a biopharmaceutical company that will include sufficient information to perform the HFACS analysis. The second assumption was that the data from such investigations existed in a current database and will be able to be queried according to human errors by functional area. Finally, I assumed that I would be able to obtain agreement from a group of operatives with expertise in human error investigations to serve as part of the review panel for the study data. I assumed that the personnel selected to assess the interrater reliability of the HFACS would have the necessary expertise and would be able to participate in an HFACS training workshop provided to assess the investigations.

Scope and Delimitations

I delimited this study to biopharmaceutical manufacturing organizations that handle drug substance products or active pharmaceutical ingredients, and I delimited the data collected to incident investigations in which human error was the central cause for deviation. In addition, I delimited the information to incident investigations within functional departments related to the manufacturing of biopharmaceutical products. The investigations evaluated covered a period of 2 years from 2013 to 2014. Because this was a reliability study, the objective was to determine the interrater reliability of the HFACS taxonomy by assessing the level of consensus among users. The study did not involve an attempt to determine the main causal factors of human error, but rather

revealed the utility of the HFACS taxonomy to these types of investigations in the biopharmaceutical industry.

I delimited the determination of whether the HFACS is comprehensive enough to cover error incidents in the biopharmaceutical manufacturing environment by users in that industry. I delimited the data to cover 161 incident reports from a biopharmaceutical manufacturing organization. The data encompassed a 2-year period and included all investigations attributed to human error. I also delimited the study to particular processes involving the bulk or active pharmaceutical ingredient manufacturing processes. I selected the active pharmaceutical ingredients manufacturing processes for the biopharmaceutical industry because they represent one of the most complex and labor-critical operations (Kayser & Warzecha, 2012). Therefore, the study included only the manufacturing and support operations commonly used in those types of business (i.e., upstream and downstream processing, quality, and logistical task functions).

Limitations

There are limitations associated with reliability studies of incident coding using taxonomies. The main limitations cited in studies are ability to generalize, availability of information, experience of participants with the taxonomies, and training (Olsen, 2011, 2013). Similar limitations affected this study.

The limitation of the availability of the data was due to using the retrospective technique. In the retrospective technique, the participants analyzed incident investigations in which the root cause of the event was human error. Therefore, the information collected from the incident was the information documented in the

investigations record. However, because the design of the study was to determine the level of consensus or agreement among coders, the information available for the determinations was similar and therefore allowed reliability. The participants had access to typical incident reports that contained the facts drawn from the investigations, along with the circumstances of the occurrence of the events, which could mitigate the limitation.

The other limitation of the study was that the participants did not have a high level of experience with the HFACS taxonomy. Although the participants selected had experience in conducting incident investigations as well as the general conditions of the biopharmaceutical manufacturing processes, they did not normally use HFACS to conduct investigations. This process aligned with other reliability studies in the literature (Olsen, 2013). Therefore, a subject matter expert in the taxonomy provided the participants with detailed training on the HFACS. The training allowed the experts in investigations to use the expanded elements in the HFACS for their analysis to create a more robust system for the biopharmaceutical manufacturing industry.

Significance of the Study

Biopharmaceutical manufacturers could use the findings of this study to decrease human errors and improve the safety and reliability of their processes. A review of the literature showed that researchers have undertaken human error studies in the aviation and nuclear power industries due to catastrophic accidents (Shappell et al., 2007). The prevalence of accidents related to human error demonstrates a need to develop theoretical frameworks for understanding what factors influenced their occurrence. In the Swiss

cheese theory, Reason (1990) identified an etiology of errors that divides the causes of human error into latent and active failures. The HFACS represents an expansion of this framework because the elements used to define latent and active failures are more specific (Wiegmann & Shappell, 2003). As a result, the HFACS has gained preeminence for the analysis of accidents related to human errors.

Apart from the multiple studies involving the HFACS, researchers in various industries have also started to consider human error as causing not only accidents but also production losses. Researchers have used the HFACS in the maritime, mining, transportation, and health care industries to investigate accidents and improve the safety of operations (Berry et al., 2010). However, as noted by Berry et al. (2010), the application of the HFACS beyond the aviation industry remains limited. Even the use of the HFACS taxonomy in the maritime, mining, transportation, and health care industries is in its early stages, and a gap in the literature exists in other industries.

Research into human error phenomena in pharmaceutical manufacturing organizations also remains limited. One of the main reasons for the absence of significant research in this area is a lack of openness by pharmaceutical companies in terms of sharing sensitive production information (Rodchua, 2009). In addition, there are no specific regulatory requirements for using human factors in the investigations (FDA, 2011). The complexity of many manufacturing processes, particularly biopharmaceutical processes, and the variability of data make it difficult to assess human error information during manufacturing investigations. Further, leaders in the pharmaceutical industry

have not faced regulatory guidance that requires them to improve upon their current understanding of human error from the perspective of human factors.

Biopharmaceutical manufacturing organizations have human operators for their critical processes; therefore, these processes are susceptible to human error. Biopharmaceutical manufacturing processes are complex and difficult, requiring multiple interactions among sophisticated equipment and human interventions (Rodriguez-Perez, 2011). This study is a first step in reducing not only the rate of human error in biopharmaceutical manufacturing operations but also the effect of the associated adverse consequences. The findings of this study may play a crucial role in the professional setting of biopharmaceutical manufacturing for regulatory agencies such as the FDA, as the findings include information that policy makers can use to develop further regulations for reducing the incidence of human error.

Industrial organizations have a direct impact on society because they are the primary sources of goods and services, employment opportunities, and economic supplies. Human errors in manufacturing organizations represent a problem, not only because of their financial costs but also because of their adverse effects on the reliability and safety of industrial products (Glavin, 2010). The health care industry creates superbly engineered products and services that are capable of providing safe, high-quality results for patients. Further, improving patient safety by reducing human error should be the responsibility of health care organizations (ElBardissi et al., 2007; Glavin, 2010). Health care errors have serious consequences in terms of human suffering and monetary burdens. Through this study, I present concrete results to aid in filling these gaps.

The findings of this study may help leaders of biotechnology manufacturing companies who participate in the health care system to reduce human error and improve the reliability of their processes. The outcome may include better working conditions for employees and safer products at lower costs. The reduction of errors could also help temper the negative social perception of drugs that could heighten general public safety (Glavin, 2010). Better management of the costs associated with drug manufacturing activities can enable the continued development of safe and accessible drugs to address society's unfulfilled needs.

Summary

Investigators have considered human errors the primary cause of many catastrophic events befalling industries. Human errors have been persistent factors in investigations into these events and have led organizational leaders to study the phenomena to make their operations safer (Shappell et al., 2007). The focus of studies of human factors has been on aviation and nuclear power organizations to help their leaders reduce the rates of accidents; as a result, research in other organizations has remained limited (Berry et al., 2010). Therefore, a gap exists in the current research in terms of the other areas in which the effect of human error can be detrimental to the public and society. The resulting lack of understanding of the essential factors or precursors of such errors precludes organizational leaders from preventing them.

This chapter contained information regarding the need to study human error phenomena in the biopharmaceutical manufacturing industry. I also developed research questions to increase the understanding of the utility of the current taxonomies for human

error investigations into biopharmaceutical processes. I created two research questions to examine the validity of the HFACS using a reliability analysis to measure the relevance of the model for the industry. This study was significant because it represented advancement in the topic of human error prevention. Likewise, the study includes additional tools for professionals in biopharmaceutical manufacturing and the means to foster better health care by making medications affordable, accessible, and innovative.

The results of an extensive literature review that includes an expansion of the human error theoretical frameworks and models, in addition to a review of the current research on the topic and emphasizing other industries, appear in Chapter 2. A discussion of the methodology and statistical procedure used to conduct the analysis is in Chapter 3. The study results are in Chapter 4, and a discussion on the implications of the findings, the recommendations for future study, the limitations of the study, and a discussion on the social change implications are in Chapter 5.

Chapter 2: Literature Review

The objective of this literature review was to examine and synthesize relevant research as it related to this study. To frame the existing gap in the literature, this study involved assessing how to use the HFACS, particularly as it relates to the human error investigation of causal factors, in the biopharmaceutical manufacturing industry. The findings from the study may provide leaders of the biopharmaceutical industry with a tool that can lead to better human error investigations and a deeper understanding of the systemic factors that promote the occurrence of failures. A better understanding of the error causal factors may lead to the implementation of preventative measures in the area, although such preventative measures are beyond the scope of the study. The following paragraphs include an overview of the literature review.

I developed this literature review following a funnel approach, starting with a link to the problem statement and the theoretical models of human errors such as the schema theory, generic error model, and Swiss cheese model. I continued by analyzing the applications of the Swiss cheese model in the nuclear power operations and further expansion into the aviation industry with the introduction of the HFACS taxonomy. I then analyzed the HFACS, particularly regarding the results of its application in multiple domains. A synthesis and analysis present how the elements for human causal factors and accident prevention from the applications of HFACS allow for opportunities for error prevention.

I also explored how HFACS relates to the health care industry, starting with medical providers and pharmaceutical manufacturing. Finally, I compared the

biopharmaceutical manufacturing processes and the HFACS studies, including how to apply the variables of human factors and their effect on society. This chapter ends with a summary and conclusion of the literature review, as well as a transition to Chapter 3.

Literature Review Strategy

This literature review includes articles from peer-reviewed scholarly journals obtained from various online research databases, including Google Scholar, ScienceDirect, ProQuest, and EBSCO libraries. Additionally, the review includes relevant books from the Library of Congress and Walden University, the University of Pittsburgh, and the University of Wisconsin at Madison libraries. Finally, the review includes articles and regulations from government regulatory bodies obtained from their official websites. It also includes an examination of articles related to the theories and models of human error. In addition, the studies involved the application and variables of the HFACS in various domains.

I used a Boolean search strategy in the aforementioned databases to identify theoretical models of human error related to the study. The search identified articles with key words and terms such as *human error theories, human factor theories,* and *human error models*. An additional Boolean search strategy served to identify references related to error taxonomies using key words and terms such as *Swiss cheese model, human error taxonomies, accident investigations, HFACS, high-reliability operations (HROs) and human factor investigations, accident investigations,* and *accident causal factors.* To locate articles related to regulations regarding human error investigations in health care and pharmaceutical manufacturing companies, the key words and terms used included

human error regulations, human factors regulations, pharmaceutical manufacturing investigations, human factors investigations, and *biologics manufacturing.* The executed search strategy produced suitable peer-reviewed references, regulations, and other relevant scholarly works to develop the literature review. The primary objective of this literature review was to locate current research on human error investigations with the use of human factors analysis and HFACS in multiple domains, particularly in the health care industry. Furthermore, the primary focus of this review was biopharmaceutical manufacturing errors.

Link to the Problem Statement

Scholars have identified human errors as key contributing factors of major disasters in history. Accident investigators have associated human elements with catastrophic events such as Three Mile Island, the Space Shuttle *Challenger*, the *Exxon Valdez*, and Chernobyl (Griffith & Mahadevan, 2011). Using formal human error classification methods is common to investigate catastrophic events in complex safety-critical systems (Altabbakh, Murray, Grantham, & Damle, 2013). Furthermore, such classification systems have proven suitable for human error investigations, and investigators can use them either to examine events retrospectively or as a preventive tool to anticipate future errors. Investigators achieve the retrospective or prospective analysis of human error through using formal human error taxonomy tools such as the HFACS based on modes to identify errors that could potentially occur during task performance. The HFACS has become a popular error analysis tool for the aviation industry as well as for other domains (Salmon et al., 2011; Salmon, Cornelissen, & Trotter, 2012). Although

there is limited literature in domains outside the aviation industry, researchers have recently examined the HFACS and its application in other fields.

Similarly, the incidence of human error has adversely affected the health care domain, including the manufacturing of drug products, and researchers have used HFACS to examine these errors in various studies (ElBardissi et al., 2007; Hughes, Sonesh, Zajac, & Salas, 2013). Human error represents a problem in the manufacturing activities of pharmaceutical companies that jeopardizes the quality and reliability of their products (Collazo, 2008). This study involved examining the issue of human error in the biopharmaceutical manufacturing industry, with a particular focus on how to use the theories and frameworks to understand the underlying factors that promote errors in that domain. In this literature review, I examined recent research in the area of human error investigations, as well as theoretical frameworks and models, to study the incidents.

Human Error Theoretical Frameworks

Scholars have proposed various theories of human error within the existing literature to describe the drivers of accidents. The focus of early psychological inquiries of human error was on the mental and behavioral aspects of the phenomenon, particularly in the cognitive domain (Reason, 1990). Accordingly, from a behavioral perspective, scholars considered human error to be actions prompted by a response. Individual performance may be the cause of actions that promote errors. The major theories of human error allow for an understanding of how failures occur, which serves as a building block for accident investigation frameworks.

Schema Theory

Many researchers have conducted studies on the causes of errors based on performance behavior in which previous mental knowledge or conceptions trigger action sequences. For instance, researchers have explained erratic human actions using the schema theory to elucidate an individual's acts (Plant & Stanton, 2013; Reason, 1990; Stanton, Salmon, Walker, & Jenkins, 2009). According to the schema theory, generic knowledge founded on past reactions or experiences organized around their perceptual organization or schemata forms the basis of the way an individual acts (Plant & Stanton, 2013; Reason, 1990; Stanton et al., 2009, 2013). Therefore, inappropriate activation of a schema or the lack of a known mode will produce a faulty action directed by the individual, thus resulting in a failure. To this end, the individual's mind and experiences are significant dynamics in the decisions that will prompt erratic actions.

In such cases, proficiency, practice, and expertise with the individual role can influence errors. Cognitive control is a function of the experience of the individual represented as a skill, rule, or knowledge-based behavior (Rasmussen, as cited in Reason, 2008; Stanton & Salmon, 2009). Therefore, human error events are the result of responses from perceived data that can be highly automatic and grounded in an individual's skills, associations, or rules. However, the sequence of errors can involve more than one person, particularly in an organizational setting.

Generic Error Model (Organizational Perspective)

The basis of the generic error modeling system is the theories of behavior responses centered on skills, rules, and knowledge. Using the generic error modeling

system, Reason (1990, 2008) classified three broad groups of errors: the skill-based errors as slips and lapses grounded in automatic actions or execution, rules-based mistakes involving procedural steps, and knowledge-based errors arising from interpretation and evaluation. The generic error modeling system shows that individuals' preconditions and experiences with the schemes influence the information among the individuals involved in the failures. This understanding differs from previous models that considered the individual to be only a single dimension of the error source.

Theoretical models of human error that have a single dimension as their focus primarily center on either the individual operator or the system failures. As noted by Salmon, Lenné, Stanton, Jenkins, and Walker (2010), human error models are either person or system approaches depending on the interactions examined. However, the preferred model for error investigation must include factors beyond cognition or memory slips and lapses and focus on a combination of system-wide conditions for error examination. Examining the gap in the literature revealed that an effective model for examining human error should consider failures at various levels within the organization or the interactions of various individuals in a sequence of activities.

The result is a shift away from researching error from the individual's perspective to examining operations in the broader organizational context. For instance, a productive system results when uneventful and capable operations occur as individuals work harmoniously in a systematized arrangement (Reason, 1990, 2008; Wiegmann & Shappell, 2003). The elements of a productive system are in Figure 2. The constituents of the productive system, including the decision makers; managers; preconditions such as

facilities, equipment, and environment; and personnel work together around a system of defenses to maintain flawless execution. The logistics of an organization protect the integrity of operations under the structural controls.

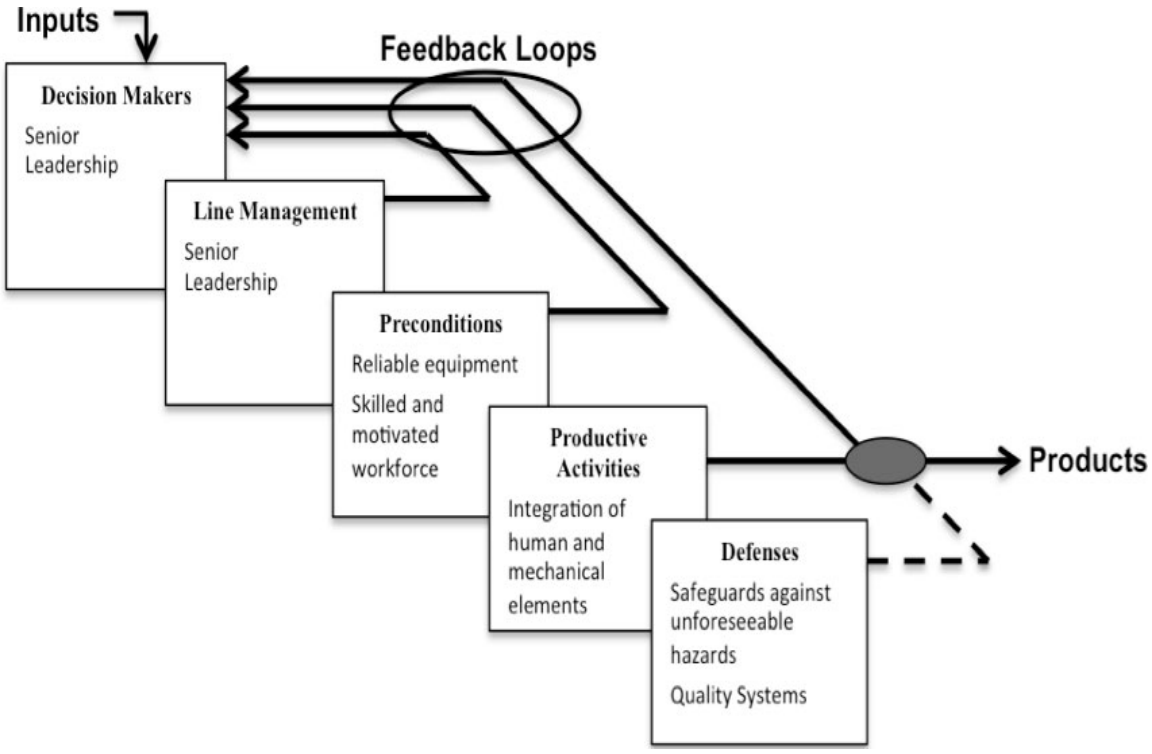

Figure 2. Productive system diagram. From *Human Error* (p. 200), by J. Reason, 1990, New York, NY: Cambridge University Press. Copyright 1990 by Cambridge University Press. Adapted with permission.

Leaders must take the organizational parts necessary to maintain a productive system into consideration when designing the functions of the operations with an emphasis on communication. Efficient design systems should consider all the factors of the operations, including mitigating actions for unforeseeable events (Raheja & Gullo, 2012; Reason, 1990, 2008; Salvendy, 2012; Wiegmann & Shappell, 2003). The productivity of the company and elimination of errors depends on how well all the

defenses and feedback loops operate according to expectations. However, a perfect and flawless production system is not the norm, and problems sometimes arise. The organizational perspective provides the explanations for a perfect system, but any system has gaps that cause errors.

Swiss Cheese Causal Factors Model

The Swiss cheese model is a representation of the problems caused by the gaps in a productive system. The Reason (1990) Swiss cheese model of accident causation (see Figure 3) presents the effect of causal failures in productive systems. In the model, the failures of the different parts of the production systems are the holes in the cheese (Reason, 1990, 2008; Shappell et al., 2007; Wiegmann & Shappell, 2003). The model shows that defenses can lose effectiveness in sustaining a consistent and productive process; therefore, the holes represent the vulnerabilities of the organization. The model also provides an explanation of the interactions of the vulnerabilities among the system components that lead to failures in latent and active levels that can align to produce a catastrophic event or accident.

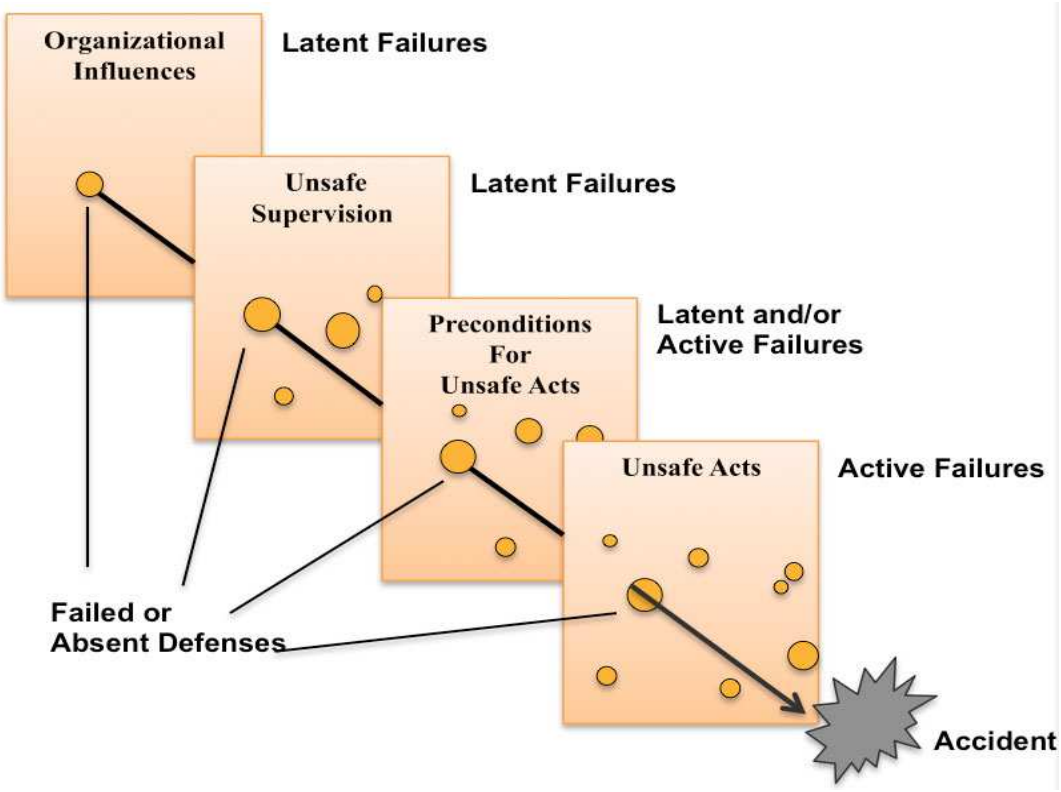

Figure 3. The Swiss cheese model. From *A Human Error Approach to Aviation Accident Analysis* (p. 47), by D. A. Wiegmann & S. A. Shappell, 2003, Burlington, VT: Ashgate. Copyright 2003 by Douglas A. Wiegmann and Scott A. Shappell. Adapted with permission.

The Swiss cheese model is one of the most relevant investigative methods used for accident investigations in various industries. The model has widespread applications so practitioners can expand investigations beyond individual or active failures to applicability in complex systems and their interactions (Altabbakh et al., 2013; D. S. Kim & Yoon, 2013; Peck, 2013). The model demonstrates that accidents are the outcomes of various causal factors subdivided into latent and active conditions. Accordingly, scholars have used the model to determine accident causations based on the contributing factors at all organizational levels. This holistic view is possible because the layers include the individual in the active failures and unsafe acts, as well as the organizational elements

such as supervision and organizational influences (Altabbakh et al., 2013). Because the model tracks the causes of actions at various levels of the organization, it also challenges the reliability of the organization rather than blaming the individuals involved in the errors.

For instance, the investigation of the Space Shuttle *Challenger* explosion in 1986 showed that the pilots or crewmembers were not responsible for the error that caused the catastrophic outcome. Using the Swiss cheese model to analyze the disaster, investigators determined that the main cause was poor decision making at the upper management level (Altabbakh et al., 2013). Furthermore, a sequence of causal factors occurred in the events that caused the explosion, including problems with the safety programs, budgetary constraints, and pressures to launch (Altabbakh et al., 2013). The investigators did not examine the latent conditions in the process to identify the associated risks and preventative actions needed. Furthermore, the investigators did not consider the defenses to prevent accidents during the launch process, including the reliability of the organization and leadership.

The reliability of an organization is dependent upon the strength of the defenses and systems to identify and prevent the effect of latent conditions. As noted by Altabbakh et al. (2013), latent conditions can be present at all levels of the organization and may be difficult to identify because they may emerge as lack of training, poor design, inadequate supervision, and unnoticed defects in manufacturing. Many organizational leaders then seek to improve organizational performance by increasing the level of

reliability; in terms of the Swiss cheese model, the organizational leaders attempt to identify the holes in the systems and present the alignment.

High-Reliability Operations (HRO)

As part of their accident investigation and reduction program, leaders of nuclear power organizations developed the latest version of the Swiss cheese model for accident causation driven by public concern over nuclear accidents caused by operators in the United States. The nuclear power operations applied the elements of the Swiss cheese model to form the HROs with the objective of conducting high-quality procedures for longer periods without the presence of errors (U.S. Department of Energy, 2008a, 2008b; Wu et al., 2009). With a more robust and efficient system, leaders of nuclear power organizations provide the expected services while protecting stakeholders from hazards.

Stakeholders, including customers, employees, and management, are an integral part of organizations. They play important roles in achieving the levels of reliability required to maintain the safety of nuclear operations. For instance, people are fallible, and even top employees make mistakes; however, organizational actions and processes influence individual performance (Peck, 2013). Accordingly, leaders can encourage operators to achieve higher performance by providing them with organizational processes that increase their understanding of the situations that generate errors to help them learn from past events.

The organizational perspective includes programs that incorporate the standpoint and support of all groups working together collaboratively. The organizational process identified by the nuclear power operations incorporates human performance factors from

all stakeholders, but management provides the primary support; in particular, these factors include training, a model for investigations, and an environment that allows for open communication (Eubanks & Mumford, 2010; Peck, 2013; U.S. Department of Energy, 2008b). Organizational influence through management support and participation strengthens the information sharing nurtured by individuals who trust leadership. The resulting environment prevents incidents of blaming operators while considering more systemic issues, including near misses during error investigations.

Investigations in highly reliable operations evaluate all causal factors in all organizational parts, rather than the specific elements of the event. Researchers of nuclear power operations have indicated that increasing the understanding of human error precursors at all layers of the operations and focusing the defense barriers on near-miss evaluations help to direct the investigation process toward accident avoidance (Salmon et al., 2010; U.S. Department of Energy, 2008a). A proper analysis of near misses from a systemic causal point of view makes the defenses against future accidents stronger by providing a higher level of awareness of the hazards present. Reducing the number of near misses may lead to a decrease in the number of failures resulting from accidents.

Despite the effectiveness of the Swiss cheese causal factors model in the nuclear power industry in increasing reliability while reducing accidents, the model lacks specificity to allow applicability that is more flexible in other domains. The model lacks an ability to identify failures in barriers or absent defenses, thereby limiting the transferability to multiple domains (Kotogiannis & Malakis, 2009; Salmon et al., 2010; Shappell & Wiegmann, 2009; Wiegmann & Shappell, 2003). Thus, the model does not

specify the holes, their size, their extent, or the relations among the causal factors of accidents. As a result, researchers have developed models to analyze the gaps in the defenses to develop a better understanding of the causal factors of many accidents.

Human Factors Analysis and Classification System (HFACS)

The Swiss cheese model lacks information on the factors that cause the failures in the systems. To expand the knowledge of the causal factors or the holes of the Swiss cheese model, Wiegmann and Shappell (2003) examined aviation accidents to understand the causal factors for aviation systems. The researchers studied each defensive layer and classified the unsafe acts and latent conditions in a taxonomy with four main tier categories, as presented in Figure 4. The categories align with the Swiss cheese model in which causal influence follows in succession and includes specific factors for each category from organizational influences to the individual level in unsafe acts.

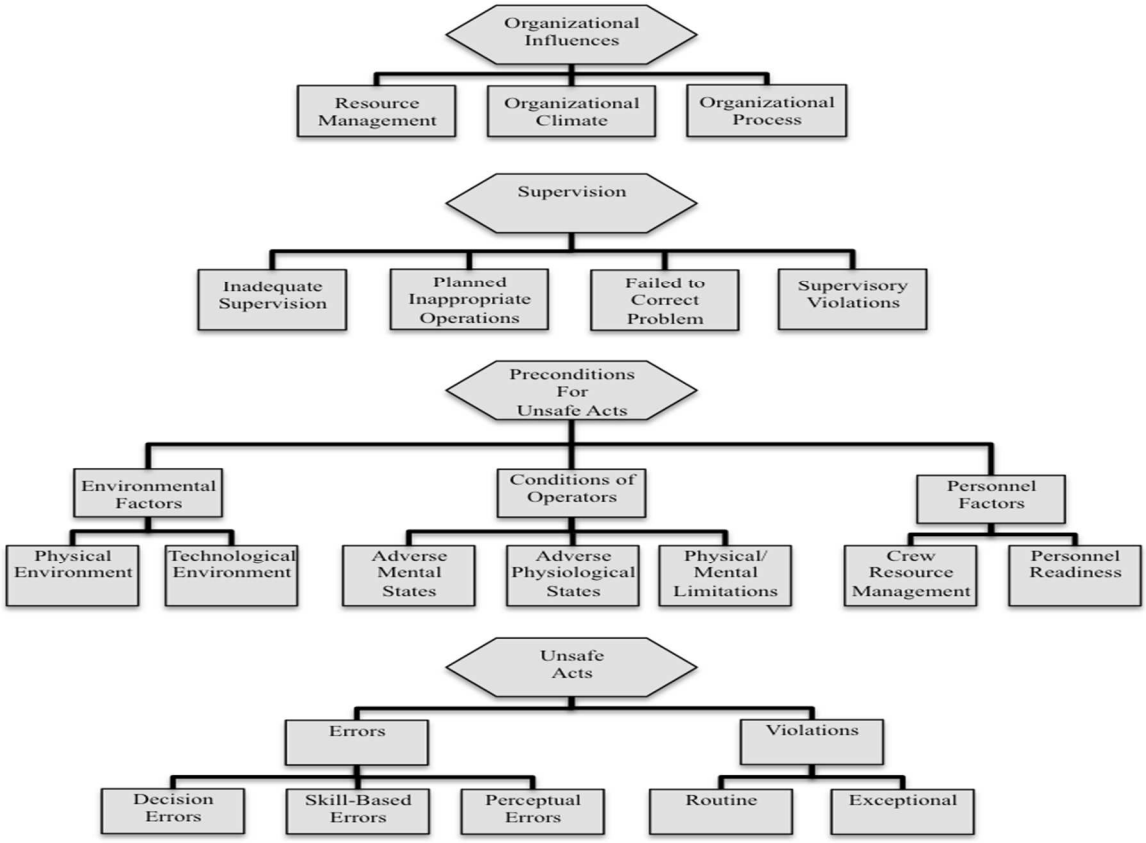

Figure 4. The HFACS taxonomy. From *A Human Error Approach to Aviation Accident Analysis* (p. 71), by D. A. Wiegmann & S. A. Shappell, 2003, Burlington, VT: Ashgate. Copyright 2003 by Douglas A. Wiegmann and Scott A. Shappell. Adapted with permission.

The HFACS taxonomy provides tools that allow aviation accident investigators to identify the active failures more systemically, including the interactions between the various levels of the organization. Researchers have demonstrated that the HFACS allows examinations of the failures causing the accidents, as well as interactions among causal factors (Belland, Olsen, & Russell, 2010; Berry, 2010; Berry et al., 2010; Paletz, Bearman, Orasanu, & Holbrook, 2009; Patterson & Shappell, 2010; Walker et al., 2011;). Therefore, the HFACS is suitable as a predictive tool for human error accidents because it can identify the linking factors between latent and active conditions. The association of

factors allows the HFACS to become a preventive tool for increasing the safety of operations.

HFACS Applications

Accident investigators have used the HFACS as a preferred investigative tool for examining the human contributions and causal factors of accidents caused by human errors in many domains. Researchers have applied the HFACS taxonomy for the classification of errors in accidents in several fields, including the military (Walker et al., 2011), air traffic control (Moon, Yoo, & Choi, 2011), maritime (Celik & Cebi, 2009; Chauvin et al., 2013; Schröder-Hinrichs, Baldauf, & Ghirx, 2011), mining (Lenné, Salmon, Liu, & Trotter, 2012; Patterson & Shappell, 2010), and railroad industries (Baysari, Caponecchia, McIntosh, & Wilson, 2009; D. S. Kim & Yoon, 2013). The results from these studies provided strong support for the function of taxonomy to improve the human error investigations of other domains.

The use of the HFACS in other domains has also generated variations based on the needs of the particular organizations. Because the HFACS is general and nonspecific, investigators can tailor it to other domains (D. S. Kim & Yoon, 2013; Walker et al., 2011). An example of diverse derivatives of the HFACS is in Table 1. The researchers adapted the particular requirements for the needs and regulations of the domains. For instance, one of the most common adaptations of the maritime shipping industry includes adding a fifth category to evaluate the effects of external factors that can include regulatory or government influences (Chen & Chou, 2012; Chen et al., 2013). Chen et al. (2013) studied the need for additional categories involving external intrusions in open

systems such as the railroad and aircraft industries rather than closed systems such as nuclear power plants or hospitals. Furthermore, the abundance of adaptability has allowed researchers to conduct critical analyses of the modes of applications to other domains, although the level of studies is limited.

Table 1

HFACS Derivatives

Derivative	Field of Study	Reference
DoD-HFACS	Military	Walker et al., 2011
HFACS-ADF	Aviation: Australian	Olsen & Shorrock, 2010
HFACS-STAMP	Aviation	Harris & Li, 2011
HFACS-MA	Maritime	Chen et al., 2013
HFACS-RR	Railroad	Baysari et al., 2009; D. S. Kim & Yoon, 2013
HFACS-ME	Maintenance	Rashid, Place & Braithwaite, 2010
HFACS-ATF	Air traffic control	Moon, Yoo, & Choi, 2011
HFACS-MI	Mining	Patterson & Shappell, 2010
HFACS-MSS	Machinery spaces on ships	Schroder-Hinrichs et al., 2011

Note. DoD = U.S. Department of Defense. HFACS = human factors analysis and classification system.

Despite the limitations in current research with the use of the HFACS taxonomy and its derivatives in various domains, researchers have pointed to some advantages of the uses. For instance, the HFACS taxonomy is easy to use, provides a consistent structure for analysis, and is comprehensive as it encompasses multiple levels of the system (Stanton et al., 2013). The general components of the HFACS taxonomy as well as the ease of adaptability to other domains allow for a uniform and well-defined analysis of errors. Using the HFACS taxonomy, investigators can accomplish accident

investigations by compiling the causal factors observed or the error contributing factors in an organized manner.

Error Contributing Factors

One of the main advantages of the HFACS is that investigators can compile the results in the core error categories of the taxonomy, allowing for a deeper examination of the causal factors. The HFACS includes all the theoretical knowledge of human factors, from the lower level individual errors to the higher level supervision and organizational errors (Stanton et al., 2013). The HFACS allows practitioners to investigate the specific categories that are likely to cause issues and errors. In addition, practitioners can focus on determining the factors most predominant in the investigations and on whether any correlations exist among them.

In the research conducted using the HFACS in aviation, the causal factors associated with skill-based errors and violations were the most prominent cause of accidents. The studies of aviation conducted in the United States (Shappell & Wiegmann, 2009), as well as outside the United States (Lenné, Ashby, & Fitzharris, 2008), have shown that skill-based errors caused the majority of accidents. Furthermore, when analyzing the accidents in terms of fatality, data showed that violations were responsible for the majority of the lethal accidents (Shappell et al., 2007). Researchers have since compared these results from the aviation industry to other domains to identify the causal factors of accidents.

The results across other domains aligned with those of the aviation industry for accident causations. For instance, studies in the maritime, railroad, and mining industries

revealed that skill-based errors were among the main causes of accidents (Baysari et al., 2009; Celik & Cebi, 2009; Patterson & Shappell, 2010; Read, Lenné, & Moss, 2012). Even though each industry is different in its operations, the human element is considerable in the causal factors among them; however, investigators also observed additional factors when using the HFACS in other domains.

For example, when evaluating accidents in other fields using the HFACS, contributing factors from the organizational and supervisor categories emerged. In a study of mining accidents, Patterson and Shappell (2010) observed that inadequate leadership was a main causal factor for accidents. In addition, studies conducted in the railroad industry created an additional category of outside factors including regulatory elements and how leaders in the industry operate in their decisions, as well as incorporating resource management and adverse mental stage types to the preconditions tier; however, human failure of the operator occurred in the highest percentage of accidents (Baysari et al., 2009; D. S. Kim & Yoon, 2013). In other domains such as air traffic control (Kotogiannis & Malakis, 2009) and computer data entry (Barchard & Pace, 2011; Bergeon & Hensley, 2009), the predominant categories from both domains observed were skill and decision errors. However, human errors are not random events, and investigators can attribute them to a combination of causes or contributing factors.

As a result, when evaluating accidents using causal factor taxonomies, researchers demonstrated the presence of relationships among the causes. For instance, in a study of aviation accidents, researchers identified a relationship between the two causal category layers, decision errors and skill-based errors, with organizational, administrative, and

human crew violations (Shappell et al., 2007; Shappell & Wiegmann, 2009). In addition, researchers have evaluated the associations among error causal factors in the various category levels of other domains.

In mining industry studies, results have indicated the presence of a combination of factors. Patterson and Shappell (2010) identified skill-based errors and decision errors as the most prevalent, with associated preconditions of communication and the physical environment as well as unsafe leadership; all these conditions contributed to 62% of the errors. Furthermore, Patterson and Shappell found relationships among knowledge-based errors with training and qualifications as well as rules-based errors. Studies in other domains indicated relationships exist among factors in health care operations; for instance, physical and mental limitation may be a precursor for a skill-based error, a decision error, a routine violation, or exceptional violations (ElBardissi et al., 2007). Also, a multi-industry analysis of causal factors evaluating cases of food industry, maintenance, mining, and show entertainment accidents revealed relationships among the latent conditions and active failures. In particular, an association existed between decision errors and crew resource management (CRM; Berry et al., 2010). The importance of relationships to error analysis is a significant component of HFACS error examinations.

Even though researchers have used the HFACS in studies in industrial and operational domains, the existing research remains limited. Researchers have applied the HFACS in examinations of accidents in areas such as construction (Garrett & Teizer, 2009; Hale, Walker, Walters, & Bolt, 2012), mining (Patterson & Shappell, 2010; Shi,

Jiang, Zheng, & Cui, 2011), automotive manufacturing (Reyes-Martínez, Maldonado-Macías, & Prado-León, 2012), water production (Wu et al., 2009), oil refining (Gholi-Nejad et al., 2012), and industrial maintenance (Aju-kumar & Gandhi, 2011; Noroozi, Khakzad, Khan, MacKinnon, & Abbassi, 2013). A limitation of all the studies was the examination of a small number of accidents using the HFACS taxonomy to identify their underlying causes. The results from the industrial studies showed that the HFACS taxonomy is a viable methodology for accident investigation but failed to show rigor, which raised validity concerns.

HFACS Limitations

Some researchers have questioned the reliability and validity of the HFACS taxonomy in identifying the causal factors of errors. Olsen and Shorrock (2010) challenged the level of agreement among several error investigators when using a modified model of the HFACS but were not able to prove or disprove the reliability of the instrument of the HFACS taxonomy. Olsen and Shorrock were not able to confirm or contradict the reliability of the adapted taxonomy when applied to investigations on air traffic controllers' errors. Although there is substantial reliability for using the HFACS tool in aviation, the information in other domains is limited.

One of the main issues identified in the literature was the lack of solid studies on the HFACS and its derivative forms. According to Olsen (2011), multiple researchers have used unacceptable or questionable methodologies for reliability; these studies often lack statistical significance and independent reviews, as they are primarily components of graduate studies (Olsen, 2011, 2013; Olsen & Shorrock, 2010). Furthermore, multiple

HFACS studies have included the contributions of the taxonomy, which may denote a lack of independence (Olsen, 2011). The reliability of the HFACS studies relates to the ability of the coders to validate whether they can have reproducibility among individual coders and the lack of statistical significance. Conversely, the proliferation of the HFACS taxonomy and its derivatives is continually expanding the availability of data regarding the reliability of the taxonomies.

Despite questions regarding the reliability of the HFACS in the literature, researchers and practitioners continue to use the HFACS. For instance, U.S. Department of Defense researchers identified the HFACS taxonomy as useful in determining the associations of causal factors by providing for usability as well as potential for investigations that can predict errors (O'Connor, Cowan, & Jeffrey, 2010; O'Connor & Walker, 2011; O'Connor, Walliser, & Philips, 2010; Walker et al., 2011). Furthermore, researchers have evaluated the reliability of the HFACS in various studies by identifying a proper agreement among raters based on Cohen kappa values of .60 to .74 (Ergai, 2013; Harris & Li, 2011; Li & Harris, 2005; Wiegmann & Shappell, 2003). In addition, various researchers have identified a variety of significant causal factor pairs and reported a significant chi square value ($p \leq .001$) and a significant odds ratio ($p \leq .01$), thus indicating the validity of the taxonomy (Berry et al., 2010; Stanton et al., 2013). Nevertheless, researchers of studies on the use of the HFACS have provided significant knowledge to improve the safety of operations.

Organizational Implications

As previously discussed, the main causal factors in the active failures tiers relate to the latent conditions of the organization and supervision. Similarly, studies have shown that CRM training, knowledge, and experience had the greatest influence on error and operations (Arthur et al., 2011; Kotogiannis & Malakis, 2009). Training and CRM provide an understanding of how organizational management and employees have a direct effect on the causal factors of errors and, more important, how human attitudes can play a key role in error detection.

Developers of the most successful organizational programs such as HRO and CRM have established that to identify errors and precursors, the workers and management need to cooperate to achieve a culture of collaboration and openness. Error management and CRM training address the mindset factors that may affect error detection, such as behaviors that promote errors (Arthur et al., 2011). Furthermore, the focus of CRM is to eliminate errors by emphasizing the performance of the team rather than of the individual (Kanki, Helmreich, & Anca, 2010). As a result, investigators evaluate the errors not from an individual perspective but from a system point of view. The result is a culture in which assigning blame is not the main objective of the error investigations.

The focus of the team members in CRM is to be vigilant and aware that errors can occur; as a result, team members seek signs of fatigue, abnormal behaviors, or stress that can promote accidents. In the aviation domain, organizational leaders seek to instill alertness to prevent errors by developing appropriate attitudes and encouraging the

courageous behavior of speaking up by critiquing oneself, cross checking team members, verbalizing routine actions under a high workload, and consciously repeating back instructions (Kanki et al., 2010). Team members become familiar with their colleagues' challenges and scrutinize their actions to detect potential mistake conditions. These practices result in a culture of open communication and can lead to fewer errors or errors detected in a timely fashion.

The basis of the organizational practices of the CRM and HRO organizations is the open and blame-free culture founded on rigorous standard procedures. The standard operating procedure defines the working activities of the team, including communication and decision making (Kanki et al., 2010). By following the standard procedure, the whole team knows the functions and actions each member must follow, which reduces the possibility of mistakes. The primary responsibility of performance and adherence to the procedure belongs to the team leader or, in the case of the crew, the captain. Although each organization is unique, leaders shape the culture and define whether they promote high reliability and safety as their primary objectives.

Human Errors in Health Care

The issue of reliability and safety due to the occurrence of human errors in health care is significant and considered a major cause of deaths in hospitals. More people die in hospitals due to medical errors every day than from HIV/AIDS and road traffic accidents (Runciman et al., 2007; U.S. Department of Health and Human Services, 2013). In recognition of this issue, health care authorities and practitioners have requested that health care institutions report human errors to authorities (London Medicines and

Healthcare Products Regulatory Agency, 2012). For this reason, practitioners in medical institutions seek human error reduction tools so they can mitigate the effect on patients.

As a result, medical error investigators have used human error theories and taxonomies extensively in many areas of the health care field to examine the causal factors. For instance, medical error investigators have used human error theories and the HFACS in the most critical areas of medical institutions, including intensive care units (Bion, Abrusci, & Hibbert, 2010; Elliott, Page, & Worrall-Carter, 2012), operating rooms (Bosma, Veen, & Roukema, 2011; Catchpole et al., 2007; Diller et al., 2014; ElBardissi et al., 2007; Wiegmann & Dunn, 2010), emergency rooms (Bleetman, Sanusi, Dale, & Brace, 2012; Itoh, Omata, & Andersen, 2009), medication (Hughes et al., 2013; Werner, Nelson, & Boehm-Davis, 2012), nursing (Armitage, 2009), and informatics (Cacciabue & Vella, 2010). Results from the studies revealed that researchers have found causal factors similar to those observed in aviation and other domains in the majority of health care areas.

In operating rooms and during cardiovascular surgeries, practitioners who study errors can use the HFACS to identify the latent and active conditions as well as the correlations of the causal factors of errors. Skill-based failures were the most common type of unsafe act observed, along with supervisory and planning errors, especially in the form of too many tasks performed at the same time (ElBardissi et al., 2007). ElBardissi et al. (2007) demonstrated that the HFACS is a tool that enhances medical error investigations, as it incorporates factors not commonly examined, including latent and active failures. Studies of human factors in the area of health care have shown that the

interventions identified in other domains such as aviation and nuclear operations will not function alike in the health care field.

In health care, errors do not affect the medical staff in the same manner as errors affect personnel involved in other domains such as nuclear power organizations or mass transportation. For instance, in aviation, lives are in danger when errors occur, and the culture promotes open reporting with limited immunity, protection of the parties involved, and anonymity (Ricci, Panos, Lincoln, Salerno, & Warshauer, 2012). In contrast, identifying errors or near misses in the health care field can have personal implications for the medical staff, as practitioners fear for their reputation, legal implications, and questions regarding their expertise (Dekker & Nice, 2013; Faltin, Kenett, & Ruggeri, 2012). Furthermore, as noted by Dekker and Nice (2013), a just culture is not the same for all health professionals, as it represents a predicament with accountability for medical errors. The resulting culture demonstrates no communication of errors or near misses because of fear due to negative or adverse implications. For leaders of health care institutions, the main challenge is to implement a just culture that protects all stakeholders, including patients and medical staff.

The organizational elements of CRM become more relevant in medical institution settings, as all stakeholders need to stimulate the culture under the direction of the organizational leadership. As noted by Smith (2010), organizational leaders who promote a just culture by fostering the courageous behavior of employees speaking up require adequate training in all fundamentals, with patient safety as the principal goal. The CRM aspects applied in medical settings will support teamwork and eliminate the

fear of blame in reporting incidents and behaviors. The existence of fear among management leads to a blame culture, which is the main requirement for identifying the latent causal factors or error precursors that challenge the applicability of the HFACS or the HRO system.

Medical practitioners have not entirely accepted the direct relevance of the aviation human error investigational and prevention practices to the medical field. According to Ricci et al. (2012), although aviation tools expand the understanding and prevention of medical errors, there are many differences among the domains, such as regulations and operating settings. Conversely, many commonalities exist between aviation and health care, particularly the rapidly changing situations that predispose individuals to errors, such as high turnover of patients, time constraints, diversity of clinical cases, shift work, and stress (Bleetman et al., 2012; Mansour, James & Edgley, 2012). Although the conditions of aviation and health care may not match precisely, applying the HFACS to recognize and prevent errors increases the opportunities of benefit to patients and medical staff.

Regulatory bodies have recognized the importance of reporting human errors as well as near misses. As an example, researchers at the London Medicines and Healthcare Products Regulatory Agency (2012) noted that in the area of blood transfusions, leaders in medical institutions reported anxiety and execution assumptions caused 50% of the 3,000 errors, including 1,000 near misses. Although the leaders of regulatory agencies are requesting error reporting from medical institutions, the error types requested only include categories such as incorrect process, incorrect procedure, procedural steps

omitted, lapsed or no training, inadequate training, ineffective training, rushing, concentration lapse, and communication (Langham, 2012). The error categories requested are primarily in the active or individual area, which misses causal factors in latent conditions, as presented by the HFACS in Figure 3. Although the leaders of regulatory agencies in the health care field are requesting error investigations and reporting, they are not using human factor analysis to determine the source.

Human Errors in Pharmaceutical Manufacturing

The pharmaceutical manufacturing industry is another complex, highly technical, and regulated component of the health care domain that is vulnerable to human errors and can benefit from the theoretical frameworks previously discussed. Leaders of regulatory agencies require that leaders in pharmaceutical manufacturing companies identify errors and deviations by conducting investigations according to the regulatory agency requirements. Specifically, as noted by Rodriguez-Perez (2011), FDA leaders require that the members of the quality control unit review records to confirm that errors did not occur during manufacturing or, in the case of errors, to investigate the cause of the occurrence. Furthermore, one of the primary causes for regulatory observations during FDA inspections in pharmaceutical companies is the lack of adequate investigations for deviations during manufacturing operations (Rodriguez-Perez, 2011). The companies are still not effectively meeting the requirements of the regulatory agencies by properly investigating the process deviations, as they are not determining the source of the errors.

Investigations in the pharmaceutical industry are deficient and lack the ability to identify both the root cause and the necessary corrective actions. A report from the FDA

on pharmaceutical manufacturing indicated that human factors were present as a cause for deviations or drift in manufacturing processes (Friedman, Smedley, Torbeck, & Santiago, 2011). The pharmaceutical regulations require that organizational leaders reduce variability in their operations and procedures by implementing corrective and preventative actions based on the root cause of investigations. However, many company leaders are still failing to identify the root cause before they implement corrective actions. For example, approximately 80% of the investigations in the pharmaceutical industry cited human error as the root cause and thus leaders implemented operator retraining as the corrective action (Collazo, 2011). This finding demonstrated that investigations lack the theoretical fundamentals previously discussed, as human error should be an outcome rather than a cause. The resulting corrective action of retraining is inadequate because it fails to address the root cause.

Another problem with the current error investigation process in the pharmaceutical industry is an emphasis on process optimization. The focus of typical investigation process in such organizations is process optimization tools and problem-solving techniques designed for production industries rather than looking at causal factors (Korakianti & Rekkas, 2011; McCormick & Wylie-McVay, 2012; Myszewski, 2010, 2012). The focus of these investigations was on identifying the parts of the process that fail based on the assumption that correcting a part of the process will stop the error. The result of such an investigation is an ineffective corrective action because, as in the case of human error, it will focus on failure at the individual level rather than combinations of factors.

To improve the investigations related to human error, leaders of pharmaceutical organizations are expanding root cause analysis in the active failure categories. For instance, human error investigations have expanded to identify errors in the categories of active failures, including omission, slips, memory lapses, and mistakes (Wachter & Yorio, 2013). The resulting investigations expand the examinations for errors as a cause of the active failure as well as to incorporate precursors of such errors. However, the human investigations process is still lacking, as investigators do not consider latent failures to be error precursors.

Although the literature of human error investigations in the pharmaceutical industry using causal factors is lacking, some researchers have used the concept of the Swiss cheese framework. Researchers used error modeling and causal factors to investigate human error in analytical test results in quality assurance laboratories (Kuselman, Pennecchi, Fajgelj, & Karpov, 2013). Kuselman et al. (2013) suggested the taxonomy of defensive layers, including latent and active conditions in the validations of the analytical method, the training of analysts, quality control, and supervision. A limitation of the study was Kuselman et al.'s (2013) use of laboratory testing and their presentation of only a proposal of the model, which therefore lacked application to real cases. In addition, the study had the same limitations previously identified for the Swiss cheese model, in which a taxonomy to classify the specific failure conditions was missing.

Many researchers studied the use of aviation-derived taxonomies for applicability in pharmaceutical manufacturing settings. For instance, Konstantinos et al. (2011)

studied how the existing industry regulatory requirements permit adapting the aircraft maintenance human factors taxonomy to the biotechnology and pharmaceutical industry. Konstantinos et al. found the current requirements of good manufacturing practices from pharmaceutical regulatory agencies in Europe and the United States support the implementation of human factors analysis systems. In addition, more than half of the respondents of a survey indicated the main area with the potential to cause errors was the team and organizational factors (Konstantinos et al., 2011). The study showed that the pharmaceutical and biopharmaceutical industries would benefit from using a model for analyzing errors that includes human factors in latent and active layers. However, a limitation of the study was that the researchers did not delineate a clear taxonomy and did not examine applicability into actual error investigations.

Model for Biotechnology Manufacturing Investigations

Although the research described above illustrated that human error is a significant problem, the literature review indicated that researchers have largely neglected the application of systems-based error methods for investigations within the biotechnology manufacturing field. Most important, the review of literature revealed a gap in the use of human factors analysis for the investigation of human errors in health care and pharmaceutical processes (Rodriguez-Perez, 2011). Only one study in this review included an evaluation of human factors analysis for human error in the biopharmaceutical manufacturing industry.

Konstantinos et al. (2011) conducted a study using aviation taxonomy in Europe with human factors analysis in the biopharmaceutical industry and demonstrated limited

empirical results, as the data did not include real investigations and the focus was on the regulatory environment and some elements of applicability. However, the literature identified in the field of human error indicated that investigations could benefit from a more comprehensive analysis. The review also revealed that models such as the Swiss cheese framework and the HFACS have been effective in reducing accidents and errors in many domains.

Human error investigation and corrective and preventive actions are the most commonly applied tools of error management within the pharmaceutical industry. Researchers have emphasized risk management, reliability, six sigma, or process failures rather than system conditions (Junker, 2008; Lewis, Hernandez, & Meadors, 2013; Lopez et al., 2010). The result was a focus on process quality instead of error elimination based on the identification of different driver errors and error-causing conditions in the manufacturing operations. An approach that permits practitioners to evaluate the causal factors in a systemic and proactive manner needs to drive the investigation processes.

Despite the lack of information on the applicability of the HFACS to biopharmaceutical manufacturing, the system represents a more proactive error management approach for investigations. According to the literature, researchers have not yet investigated the aviation taxonomy for human error investigations within the biopharmaceuticals manufacturing context, but the taxonomy represents an alternative that interests regulatory bodies (Konstantinos et al., 2011). Pharmaceutical industry investigators can examine human error by applying factors related to the other dimensions of the latent conditions.

Studies in the literature indicated that error investigators can use causal factors in multiple domains, including the biopharmaceutical manufacturing industry. The factors used in the HFACS taxonomy are transferrable and easy to modify for application to multiple domains (Stanton et al., 2013). In addition, the factors are general and permit modifications within four main categories: acts, preconditions, supervision, and organizational influences. However, the taxonomy must align to match the needs of the domain, which in this case was the biopharmaceutical manufacturing industry.

The biopharmaceutical manufacturing industry is complex, and its processes are susceptible to deviations that result in significant losses. Biopharmaceutical productions involve multiple and lengthy steps that run continuously and require advanced equipment for manufacturing as well as knowledgeable and skilled operators (Kayser & Warzecha, 2012). The high level of technology required from the operations and the workers necessitates an increased degree of accuracy and commitment. The resulting conditions are highly stressing, as the operators must work during shifts under pressure.

The intensity of the biopharmaceutical manufacturing operations promotes the occurrence of deviations primarily associated with human errors. According to Konstantinos et al. (2011), human errors are the result of an organization's issues and a lack of resources. Although the literature revealed a need to classify the causes of human factors, the focus of the current taxonomies for investigation is on the operator level. The focus of the causes of human errors is then a limited scope of factors.

The main factors documented at the first tier of active failures in the biotechnology industry are similar to the health care and pharmaceutical industries. The

FDA (2011) included slips, lapses, and mistakes in the causal categories of errors. In addition, researchers commonly accept that when human error occurs, the second tier of the cause generally falls into the categories of application, decision, documentation, learning–training gap, memory gap, or omission (Collazo, 2008). As demonstrated in the discussion of the medical establishment, investigations with this type of root cause include only active failures and miss the latent conditions.

To conduct human error investigations that produce real root causes that allow for the identification of preconditions and latent conditions, researchers must use a taxonomy, such as the HFACS, which will permit them to view the whole spectrum. As noted by Stanton et al. (2013), error investigators can apply the HFACS to any domain, thus allowing for a deeper analysis of the combinations of causal factors with the application of simple statistical techniques that allow for correlations among factor tiers. Investigators can therefore modify the HFACS with the current error categories used for investigation to have a more robust process. The investigation process will then be proactive in preventing errors to ensure the production of safe and high-quality products.

Having increasingly robust investigations increases the quality of the production processes while reducing losses and manufacturing costs. According to Clarke (2009), the cost associated with human errors in drug manufacturing is $30.7 billion. Also, due to the expensive and complicated nature of biopharmaceutical manufacturing processes, production losses lead to a significant financial impact that affects costs and delays in time to market (Subramaniam, 2012). The reduction of error through accurate investigations has a direct impact on the cost of health care and the timely introduction of

products to the market. Biopharmaceutical drugs play a significant role in health care and society in general.

The biopharmaceutical industry is the most active sector in developing new therapies for treating medical needs. For example, the industry has produced more than 200 new therapies since 2002 for the treatment of significant diseases such as HIV, diabetes, and various forms of cancer (Kayser & Warzecha, 2012). In addition, the drug regulatory authorities approve 10–15 new products, including new therapies, each year in the biopharmaceutical sector (Kayser & Warzecha, 2012). The innovations of the biotechnology industry are substantial and are a vital source of therapy to improve patient health. However, innovation and the availability of products are still problems.

The introduction of new products has been decreasing because of cost constraints. According to recent studies, the volume of new products since 2002 has been declining (Cuttler & Sahni, 2013; Lanthier, Miller, Nardinelli, & Woodcock, 2013). The expectation is that the high cost associated with losses due to errors will affect the funds available to companies for innovations and the introduction of new drugs. It is imperative to maintain the output of cost-effective products and therapies through more efficient and reliable manufacturing processes.

Conclusions and Transition

The theories regarding human error include the individual actions from slips and lapses as a component of a system and organization. The focus of the theoretical frameworks of human error discussed in this chapter was how individuals perceive situations and executes actions based on the conditions of schemes (Plant & Stanton,

2013). However, the knowledge and abilities attained through experience or education also influence individual schemes. Most important, human errors do not always occur because of an individual's actions based on the aforementioned schemes and knowledge but rather are the result of causal factors presented in the form of a sequence of latent and active failures.

Researchers use the Swiss cheese model to demonstrate the relations among latent and actual factors in the occurrence of accidents. Reason (1990) developed the Swiss cheese framework to aid human error investigations in examining the effect of holes in the defense barriers of the different systems in a productive organization, including unsafe acts, preconditions, supervision, and organizational influences. Although Reason designed the framework to analyze accidents in nuclear power organizations, investigators adapted it in multiple domains to investigate accidents and errors. Despite its popularity, researchers who have used the Swiss cheese model found it to be lacking in practical application, as it was not able to define failures or system breaks clearly. As a result, Wiegmann and Shappell (2003) developed the HFACS taxonomy to investigate naval aviation accidents. The HFACS taxonomy categorized the causal factors into four tiers: unsafe acts, preconditions for unsafe acts, supervision, and organizational influences (Wiegmann & Shappell, 2003). The effectiveness and success of the HFACS in evaluating aviation accidents promoted its use in other domains; as a result, it joined the Swiss cheese model in becoming one of the most used frameworks for accidents and human error investigations.

To conduct accident investigations, researchers in the various domains adapted the HFACS in derivatives to suit the specific needs of their field more effectively. Researchers have shown that the HFACS was instrumental in investigating aviation accidents worldwide in military as well as in general aviation; likewise, researchers have used it extensively in railroad, maritime, and health care investigations (Berry et al., 2010). Researchers have used the HFACS to investigate accidents and to develop interventions that can eliminate the precursors of accidents.

Despite the success and acceptance of the HFACS applications, researchers have questioned their reliability and validity. Olsen (2013) noted that the studies demonstrating the reliability of the HFACS are limited, which leads to questions about the interrater reliability of the taxonomy. Conversely, researchers in the aviation field recognized a statistical significance in the results, along with a significant reduction in accidents observed in their domain (O'Connor & Walker, 2011). Existing data did not refute the reliability of the HFACS in aviation application. Although the use in multiple domains is growing, few studies exist in domains outside aviation.

This review of error investigation literature indicated the limited nature of the everyday application of HFACS techniques in the biopharmaceutical manufacturing context. Despite this gap, human factor taxonomies used in the aviation industry are highly applicable to biopharmaceutical human error investigations and can provide a significant contribution within the manufacturing context (Konstantinos et al., 2011). However, implementing the HFACS presents some barriers that company leadership should consider. For example, organizational factors for developing a just culture are

important to create the necessary environment of blame-free principles that will allow the required communication (Bleetman et al., 2012). Creating such an environment should result in the better implementation of an error-reduction system.

A more detailed discussion of the implementation model for the HFACS in the biopharmaceutical industry appears in Chapter 3. The discussion includes the HFACS variables and quality indicators presented in this literature review, as well as an explanation of how to measure and statistically analyze them to address reliability and validity concerns. Finally, a discussion on how to apply the specific approach to research to answer the research questions regarding the implementation in the taxonomy for human error investigations in biopharmaceutical manufacturing processes, as informed by the literature review, appears in the chapter.

Chapter 3: Research Method

Human error is a part of everyday life, and people are likely to cause errors despite precautions to prevent them. The problem studied was that although individuals recognize the potential effect of human error on organizational performance, how organizational leaders can reduce the frequency of errors remains unknown. The impact of human error is substantial, as it is the leading cause of accidents and provides negative consequences for various industries, including aviation, nuclear power, transportation, and health care (Berry et al., 2010). For this reason, organizational leaders have implemented human error frameworks and taxonomies such as the HFACS to reduce or prevent errors that may lead to the loss of valuable resources, property, and even lives.

This study involved a reliability analysis to investigate the utility of the HFACS for conducting investigations in biopharmaceutical manufacturing processes. A description of the study design and an explanation for using a reliability study as the most appropriate technique appear in Chapter 3. A discussion of the population and sampling procedures, data collection approach, analysis techniques, and steps to ensure the ethical considerations for the study also appear in Chapter 3. The chapter ends with a summary regarding the research methodology and a transition.

Research Design

The reliability study involved assessing the adapted HFACS for error investigations in biopharmaceutical manufacturing processes. The research design included a detailed plan of all aspects under examination (Howell, 2010; Leedy & Ormrod, 2013). The explanation of the research design includes the methodical process

that led to valid and reliable results. I aligned the methodology of this research with the main objective of the study, which was to collect data that could provide information to determine the utility of the modified HFACS for biopharmaceutical manufacturing investigations.

Members of biopharmaceutical manufacturing industries manage multiple investigations as part of their quality systems programs. Many individuals conduct deviation investigations due to the large volume and time constraints needed to maintain business demands (Rodriguez-Perez, 2011). The investigation process entails reviewing and approving personnel in multiple functional areas, including the quality organization representative. The involvement of multiple investigators creates a need to minimize variations in the data that multiple raters will add.

Researchers have studied the measurement of variations, especially involving multiple investigators. Measuring the variation among raters involves conducting a study where a group of raters must score the same group of data (Gwet, 2012; Feng, 2013). This study provided the information necessary for quantifying the extent to which raters agree in identifying the human factors involved in incident investigations using the modified HFACS. A low interrater reliability would indicate a possible need for additional changes in the HFACS taxonomy or training to the raters (Olsen, 2011). After achieving an acceptable level of agreement, investigators can incorporate the taxonomy in the process for conducting investigations in the biopharmaceutical industry.

Various factors need consideration when designing an interrater reliability study. For instance, Hallgren (2012) recommended that interrater reliability studies consider

how evaluators will rate the subjects, frequency of rating, type of scale to use for the main variables, and the raters' training. Therefore, the current study design included a specific determination of the type of analysis of the incidents according to the human factors variables and the experience and training requirements of the error investigators. Furthermore, the experimental design aligned with the sample, data collection technique, and statistical procedures.

For this reliability study, the design was a fully crossed study. In fully crossed reliability studies, raters examine all incidents in a sample (Hallgren, 2012). In the study, both raters examined the entire incident selected for the sample of the specific area. The fully crossed experimental design was suitable for the study, as additional coverage of error investigations in the manufacturing environment was possible.

The fully crossed design was appropriate because of its statistical advantages for the study. Although the fully crossed design required a higher level of effort than a noncrossed design, it was more advantageous for the interrater reliability study, as it provided for improved and controlled estimates, and it eliminated the need for alternative statistics for data analysis. The additional effort needed to analyze all the incidents by each rater was acceptable to facilitate a more sound study. There was no limitation in the availability of incident information, but there was a limitation of the availability and time for the raters. The quantitative interrater reliability research design involved fewer resources than a qualitative design, thereby allowing the more stringent sample analysis.

The methodology chosen for this study is particular to quantitative research design. In a qualitative research study, the objective is to learn about a phenomenon by

conducting interviews or observations to find possible themes or descriptions (Myers, Well, & Lorch, 2010). This study included particular variables and a statistical analysis to derive the assumptions. The variables included the factors in the HFACS selected by the raters as present or not present. The conclusions in a quantitative research method involve interpreting and deducing the data (Myers et al., 2010). The two research methods also differ in the presentation of the data. The bias of a researcher may affect conclusions developed in a qualitative study (Bickman & Rog, 2009; Creswell, 2009). However, in a quantitative research design, the basis of the conclusions is statistical analyses that contribute to decreasing the degree of researcher bias. Other designs considered for this study were within the quantitative domain.

Another research methodology considered for this study was structural equation modeling. Structural equation modeling is a framework researchers use to examine relationships among latent and observable variables and the effects among them (Bowen & Guo, 2012). Thus, structural equation modeling serves as a tool to predict the influence of latent conditions on observed effects. Although the basis of the HFACS is the theoretical framework of latent and active failure conditions, equation modeling was not an adequate design to evaluate the utility for the biopharmaceutical industry due to the type of information available in the biopharmaceutical manufacturing incident investigations.

Available information in incident investigation is not suitable for a structural equation modeling analysis. Structural equation modeling latent variables are complex or psychological phenomena that require multiple observations of conditions (Bowen &

Guo, 2012). The researchers who collected data in the biopharmaceutical incident investigations did not consider either the HFACS or a model for latent conditions. Therefore, a study of the utility of HFACS was necessary to determine the reliability to allow further analysis of human error in the biopharmaceutical industry with an adequate taxonomy.

Researchers achieve the retrospective or prospective analysis of human error using formal human error taxonomy tools, such as the HFACS, based on modes to identify errors that could potentially occur during task performance. The HFACS is a well-established and sound error analysis tool for the aviation industry, as well as for multiple other domains (Salmon et al., 2011). Although the literature review revealed a lack of studies in domains outside the aviation industry, there is an increase in researchers examining HFACS applications. In this study, the objective was not to make predictions about outcomes but to determine whether human error investigators can use the HFACS in the biopharmaceutical industry.

Methodology

I used the methodology chosen for this study to provide information regarding the reliability of the HFACS when used for conducting investigations in the biopharmaceutical manufacturing industry. The conclusions in a quantitative research design involve interpreting and deducing the data (Myers et al., 2010). This research methodology served as the basis to derive conclusions through statistical analyses based on procedures that validated the results. This quantitative interrater reliability study with

a fully crossed design served as the research methodology used as the basis to derive conclusions through statistical analyses based on procedures that validated the results.

Population

The population of the study consisted of incident investigations from biopharmaceutical manufacturing processes. Members of the investigation department in the biopharmaceutical manufacturing industry collect investigation reports from all incident deviations and maintain a database of the information for ongoing analysis and evaluation (Rodriguez-Perez, 2011). As part of the human error investigation processes, error investigators categorize root causes in ties mainly associated to operator or procedure conditions. The FDA requires the retention of such investigation records for a period of time (FDA, 2003). The database contains more than 3 years of investigational information on incidences. I derived the general population for the study from existing investigation records in which the investigators attributed the root cause to human error in a biopharmaceutical manufacturing company in the United States.

The study involved collecting information from the narrative documentation process of a company's investigational procedure in its database. The approximate number of human error investigations generated in a year is 100 to 200 for a single manufacturing company, although specific information on the total number of investigators and number of investigators per company remains unknown due to the lack of studies in the area (Rodriguez-Perez, 2011). I subdivided the data from incident investigations from three functional areas or departments of the biopharmaceutical production process: upstream manufacturing, downstream manufacturing, and

operational services support, which include materials processes, maintenance, and engineering departments.

Sampling and Sampling Procedures

Interrater agreement and interrater reliability each represent the consistency of a particular set of ratings. To calculate either measure, researchers must obtain samples wherein two or more observers have rated the same set of observable evidence (Gwet, 2012). To obtain such samples, raters must evaluate a collection of incident reports and rate them against the HFACS. The collections of incidents that raters analyzed were representative of the processes that error investigators will use with the modified HFACS taxonomy using a sound strategy.

The strategy chosen for collecting the sample of incidents for evaluation in this study was stratified random sampling. Stratified random sampling is a methodology of sampling in which a researcher divides the population into subgroups or strata to collect random samples (Levy & Lemeshow, 2008). Furthermore, stratified random sampling is a combination of a simple sampling process with the increased reliability of obtaining information on different segments of the population (Levy & Lemeshow, 2008). This methodology was applicable for the reliability study, as the incident investigations were of errors in three functional areas of the manufacturing processes. In addition, the sampling methodology allowed the use of raters with expertise in each subgroup of the areas under study.

The subgroups for the study were human error in three functional areas or departments of the biopharmaceutical production process: upstream manufacturing,

downstream manufacturing, and operational services that include materials processes, maintenance, and engineering groups. Those groups represented the most important processes in the key functional areas conducted in manufacturing biopharmaceutical products (Rodriguez-Perez, 2011). It was important to measure the reliability of the HFACS in the taxonomy in the most important areas of the domain for the particular incidents that were of most concern. I extracted and stratified the sample of the populations in the separate functional areas.

All the incidents information was in a database containing the investigations of the entire facility. The study encompassed 2 years of incident investigations from 2013 to 2014. I collected the information from the incident investigations by conducting two separate queries of the database. The first data query was to obtain the incidents with a root cause related to human errors, which were the main interest in the study. The second query separated the error incident investigations by each of the subgroup areas of the study (operational services, upstream manufacturing, and downstream manufacturing). From each of the subgroups of incidents, I collected the investigation records based on the sampling size determination.

To assess the research questions, the study involved kappa analyses. Viera and Garrett (2005) noted that a moderate kappa value of .60 showed substantial interrater agreement. To detect if a moderate kappa value of .60 is significantly different from a kappa value of .00 (random chance) with a power of .95 and alpha level of .05, the required sample size is at least 40 items (Faul, Erdfelder, Buchner, & Lang, 2013; Sim &Wright, 2005). Therefore, both raters rated at least 50 incident investigations. The

raters assessed for the presence or absence of each of the 18 human factors in the investigations. The study involved evaluating three separate areas in the biopharmaceutical manufacturing site, which included 161 incident investigations within a 2-year period from 2012 to 2014.

Recruitment Process

I did not recruit humans as subjects for the study, as the unit of measure was the incident reports collected from archival data. However, as part of the study, I consulted with a group of experts in biopharmaceutical investigations to assess the comprehensiveness of the modified HFACS. The group of experts ran a pilot with the modified taxonomy to assess if the information translated correctly to the human errors frequently observed in the biopharmaceutical manufacturing industry.

The experts for the pilot study were investigators of biopharmaceutical manufacturing companies. The expert group who evaluated the comprehensiveness of the modified HFACS taxonomy was from a cross-company collaboration group including employees of the world's major biopharmaceutical manufacturing companies. I contacted leaders of the group to facilitate the participation of a select expert group of five individuals to assess the HFACS derivative for comprehensiveness. The industry experts had at least 10 years of experience in the biopharmaceutical manufacturing industry, including human error investigations. The letter for recruitment of the Biopharmaceutical Industry Organization Group members is in Appendix A.

For the reliability study, I selected a group of biopharmaceutical investigators, including two individuals per functional area. The raters for the reliability study had

experience conducting incident investigations in the biopharmaceutical industry. The raters volunteered to be part of the reliability study and to conduct ratings of incident investigations using the modified HFACS taxonomy. Raters of the reliability study were senior investigators with more than 5 years of experience with human error investigations in the biopharmaceutical industry. The participants of the interrater reliability study were volunteers who had completed a 2-day HFACS training process and had passed a certification test in HFACS.

Participants

I informed all experts and raters involved in the pilot and reliability studies of the purpose of the study and the information they would be providing (see Appendix A). The experts and raters received detailed information of the study and of how I would use their contributions. The first group participated in a pilot to confirm the adequacy of the modified HFACS taxonomy.

The modified HFACS needed assessing to determine if it was suitable for conducting biopharmaceutical manufacturing investigations. To evaluate the validity of human factor analysis taxonomies, investigators analyzed if they could cover the extent of the factors involved in the operations under study (Wiegmann & Shappell, 2003). To examine the comprehensiveness of the modified HFACS taxonomy, five biopharmaceutical industry experts evaluated the modified taxonomy for use in the domain. For that activity, five expert members of the Biopharmaceutical Industry Organization Group received the modified HFACS taxonomy to assess comprehensiveness.

After I revised the HFACS taxonomy based on the feedback of the expert panel, the five investigators used the taxonomy to assess human investigations in a pilot. The main purpose of the pilot was to test the comprehensiveness of the modified HFACS taxonomy before using it with the formal study group. The five members of the pilot did not participate in the interrater reliability part of the study. The pilot study involved a group of five biopharmaceutical subject matter experts in incident investigations evaluating the taxonomy. The pilot study included the evaluation and feedback from industry subject matter experts of the modified HFACS to determine if the taxonomy would be capable of measuring and covering the errors found in biopharmaceutical manufacturing processes as well as the practicality of its intended use.

Archived Data

The data from the incidents selected for the interrater reliability study were within a confidential database pertaining to a biopharmaceutical company. I requested permission from company leaders in a letter (see Appendix B). The information from the biopharmaceutical company, as well as all the information collected during the study, will remain confidential. I did not collect information from the company database until I received full authorizations from the pertinent company officials. I used the specific information regarding the details of the incidents in the study, as the scope of the study solely included the reliability of the modified HFACS measured through interrater reliability. The interrater reliability information did not contain specific information from the wording of the incident investigations.

Only I had access to the information collected during the study. The information within the premises remained under my control. I did not share the detailed investigational information collected during this study with any person outside the company who provided the data from the reliability study.

Instrumentation and Operationalization

To conduct the analysis of human error investigations in this study, I developed a HFACS taxonomy derivative (see Appendix B). The derivative consisted of the original HFACS taxonomy main elements (Berry et al., 2010; Wiegmann & Shappell, 2003) in combination with the frameworks developed for maritime machinery spaces HFACS-MSS (Schröder-Hinrichs et al., 2011), maintenance (Hsiao et al., 2013a, 2013b), and mines (Patterson & Shappell, 2010). The modified HFACS taxonomy included operational definitions to classify human errors from the investigations.

Although information from the literature supported the HFACS modified factors, a group of industry experts vetted the modified HFACS derivative to assess its comprehensiveness. After I incorporated modifications resulting from the experts' comments in the HFACS derivative, I executed a pilot study with a small group of three investigations experts who assessed investigations to test the usability for the reliability study. The raters classified each investigation using the elements identified in the modified HFACS taxonomy in any combination, according to the information documented in the write-ups and the factors in the different categories.

To examine the research question and hypotheses, I analyzed the HFACS derivative using investigations in biopharmaceutical human errors. The focus of the first

research question was the HFACS derivative as a whole. The raters classified each incident into one or more of the following HFACS tiers: tasks/acts, preconditions, leadership or supervision, and organizational influences. The process involved analyzing each case for the presence or absence of the 18 HFACS causal factors in the tiers. The operator act tier included two errors and two violations factors. The seven precondition categories were personal readiness, teamwork, technological environment, adverse mental state, adverse physiological state, physical environment, and physical or mental limitations. The four leadership and supervision categories were inadequate supervision, planned inappropriate operations, failed to correct problem, and supervisory violations. The three organizational influence categories were resource management, organizational climate, and organizational process. The raters examined each case for the presence or absence of each category.

The raters analyzed each incident investigation for each of the 18 factor categories. If the category factor was not present in the incident, the rating was 0. If the factor category was definitively a factor in the incident, the rating was 1. I tabulated and analyzed the ratings according to the data analysis plan.

Data Analysis Plan

The research questions and hypotheses for this study were as follows:

RQ1: What is the level of agreement (Cohen's kappa) between the two independent raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes?

RQ2: What is the difference in the level of agreement (Cohen's kappa) across different areas (operational services, upstream manufacturing, and downstream manufacturing) between raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes?

The hypotheses for the research questions were as follows:

$H1_0$: The overall Cohen's kappa statistic between the two independent raters will not be substantial ($\kappa < .61$) based on the criteria set by Landis and Koch (1977).

$H1_a$: The overall Cohen's kappa statistic between the two independent raters will be substantial ($\kappa > .60$) based on the criteria set by Landis and Koch (1977).

$H2_0$: There are no significant differences between average Cohen's kappa statistics across the operational services, upstream manufacturing, and downstream manufacturing areas.

$H2_a$: There are significant differences between average Cohen's kappa statistics across the operational services, upstream manufacturing, and downstream manufacturing areas.

To answer RQ1, I examined interrater reliability for each of the 18 separate factors that comprise the HFACS model. Interrater reliability helps to determine the magnitude of agreement between two raters (Viera & Garrett, 2005). I assessed each of the 18 factors that comprise the HFACS model for interrater reliability, and I coded each of the accidents as having or not having each of the individual HFACS model factors by each of the raters.

Interrater reliability indicated the level of agreement for each individual factor. I coded the individual factors as *both specified*, *only Rater 1 specified*, *only Rater 2 specified*, or *neither specified*. The codes *both specified* and *neither specified* indicated agreement on a particular factor. Determining a kappa value involved determining the level of agreement for that factor by examining the observed level of agreement against the expected level of agreement due to chance (Viera & Garrett, 2005). Levels of agreement ranged from -1 to 1. A kappa value larger than 0 indicates a higher level of agreement between raters than expected due to chance. A kappa value of 0 represents a level of agreement expected due to random chance. A kappa value below 0 indicates a lower level of agreement between raters than what was due to chance.

I calculated a kappa value for each of the HFACS factors. The factors included resource management, organizational climate, organizational process, inadequate supervision, planned activities, failed to correct the problem, supervisory rules and regulations violations, physical environment, technological environment, adverse mental state, physiological state, physical/mental limitations, teamwork, readiness, decision, skill-based, routine, and exceptional. With 18 total factors, I calculated 18 kappa values for each functional area.

To test Hypothesis 1, I calculated the overall Cohen's kappa statistic for each incident. The overall Cohen's kappa statistic represented the average kappa statistic across the 18 individual kappa statistics derived from each of the 18 individual factor ratings. I averaged the overall kappa statistics for all 150 incidents and compared them against the standard of $\kappa > .60$ as a substantial level of agreement (Landis & Koch, 1977).

To test Hypothesis 2, I compared the overall Cohen's kappa statistic across manufacturing, quality control, and engineering services using a one-way analysis of variance (ANOVA) test with Scheffe post hoc tests. In addition, I calculated an eta coefficient (Pearson correlation between a nominal variable and a continuous variable) to measure the strength of the relationship between the organizational area and the overall kappa statistics (Hanneman et al., 2012). The calculations of the data analysis proceeded using the SPSS data package.

Treats to Validity

When evaluating the reliability of human error taxonomy, it is important to consider the elements of content validity. The modified HFACS needs to be able to cover the elements that encompass the human factors involved in error investigations (Wiegmann & Shappell, 2003). Therefore, content validity of the modified HFACS derivative in its utility for investigating the biopharmaceutical process needed to be adequate for covering the array of factors in the biopharmaceutical manufacturing environment. Although this study did not involve measuring content validity directly, the study design included elements to ensure the impact to the overall validity of the study is not significant.

The main support of the content validity of the HFACS for use in other domains is well established and supported by literature. Researchers have used the HFACS extensively in all areas of aviation, as well as other domains, with successful results (Berry, 2010; Stanton et al., 2013). In addition, multiple reliability studies have shown that the content validity of the HFACS taxonomy is adequate (Ergai, 2013; Olsen, 2013).

The basis of the modified HFACS used in this study was the literature applications for the aviation, mining, and maritime applications. The expert panel controlled the content validity of the modified HFACS and ensured the language was appropriate to the biopharmaceutical manufacturing environment.

Another concern about reliability was using kappa statistics for measuring interrater reliability. For instance, critics of kappa coefficients have identified concerns with the dependence on rater prevalence (Kottner et al., 2011). The main concern was the ability of the raters to distinguish among adjacent categories. However, the kappa coefficient served as a good tool in the study, as the validity concern had minimal implications in categorized data.

Ethical Procedures

This study did not include subjects and only included unpublished data from investigations of a biopharmaceutical manufacturing company. I informed the industry experts as well as the voluntary raters of the purpose of the study and the use of the information that they would provide, as well as the integrity of the confidentiality of such information. I explained the purpose of the research in the letter of introduction and reiterated that I would not disclose any confidential information. To ensure confidentiality of the company information, the study did not include any personal or private business information. I secured all raw data and kept information under strict control for 5 years. After I received permission from the Institutional Review Board to conduct the study (Approval number 10-22-14-0189498), the research project commenced.

Summary

The review of the research methodology and the discussion of the appropriateness of quantitative correlational research for answering the research questions and providing justification for the research are complete. The purpose of this study was to investigate the utility of the HFACS for conducting investigations in biopharmaceutical manufacturing processes. I identified the study population from investigations of biopharmaceutical manufacturing companies in the United States. The study included 161 investigations classified with human error as the root cause corresponding to the period from 2013 to 2014. The investigations included operational services, upstream manufacturing, and downstream manufacturing. A description of the method for acquiring informed consent and confidentiality, as well as the methods for data collection and data analysis procedures, appeared in Chapter 3. A discussion on the data analysis and results appears in Chapters 4 and 5.

Chapter 4: Results

The purpose of this quantitative study was to examine the utility of the HFACS for the investigation of human error and deviations in the biopharmaceutical industry to identify the factors that led to human error in biopharmaceutical manufacturing operations. Determining interrater reliability when evaluating investigations of events attributed to human errors with a modified HFACS taxonomy indicated the utility. Data gathered were from the analysis of 161 incident reports from three main areas of the manufacturing process of the biopharmaceutical products: upstream manufacturing, downstream manufacturing, and operational services. Six investigators were separated in three pairs, for each pair to analyze and rate at least 50 incident in an area of the biopharmaceutical process. The incident reports were rated using the modified HFACS taxonomy, and I determined the agreement among the raters pairs to assess the level of reliability.

The data collection and analysis led to answers for the two research questions and their related hypothesis. The topic of the first research question was the level of agreement between the independent raters with the null hypothesis to be invalidated based on the level of agreement of the Kappa value less than substantial ($k < .60$). I obtained the kappa values for the three pairs of raters by assessing each factor identified in the modified HFACS during the evaluation of the incident reports in the sample. The second research question inquire the level of correlation of the factor values among the key areas of the biopharmaceutical manufacturing processes, upstream manufacturing,

downstream manufacturing, and services that include support as well as maintenance and engineering activities.

In Chapter 4, I present a detailed description of the study, including the data collection procedures and data analyses techniques. The results of the analyses conducted when testing the hypotheses and answering each research question appears in this chapter. The chapter ends with a summary of all the results and findings.

Pilot Study

Through the pilot study, I determined the comprehensiveness of the modified HFACS to cover the main incidents in the manufacturing processes of biopharmaceutical products. With that purpose, I contacted a group of investigators from various biotechnology companies, supplied them with the modified taxonomy, and asked for feedback. The process involved various industry groups, including the Biopharmaceutical Industry Organization Group, a biotechnology forum with members from the major biopharmaceutical companies around the world. Information gathering took place during a 1-week period. Five members from the forum assessed the modified taxonomy.

Five individuals assessed and commented on the comprehensiveness of the taxonomy. All the individuals participating in the pilot had experience with human factors and conducting investigations of human errors. The average length of direct investigational experience of the participants was 12 years. All the participants were comfortable with the topic of human factors and investigations. The results obtained from the pilot were consistent among the participants.

All the participants in the pilot study agreed that the modified HFACS taxonomy is comprehensive enough to cover the array of situations encountered in the typical biopharmaceutical manufacturing processes. They agreed the taxonomy is comprehensive and suggested minor changes or clarifications to make the taxonomy simpler to use. The final modified taxonomy used for the reliability study is in Figure 5. The main change from the original HFACS taxonomy was the order of the tiers, where I changed the taxonomy to be upside down to start the investigations process with the task and end with the organizational elements at the bottom similar to the Royal Canadian Air Force HFACS (Royal Canadian Air Force, 2013). Another suggestion was to increase clarity in the task/actions and leadership and supervision to include the word *violation*. Finally, in the task/actions tier, a pilot participant suggested changing the word *decision* with *knowledge* to prevent confusion regarding violations that are decisions from individuals.

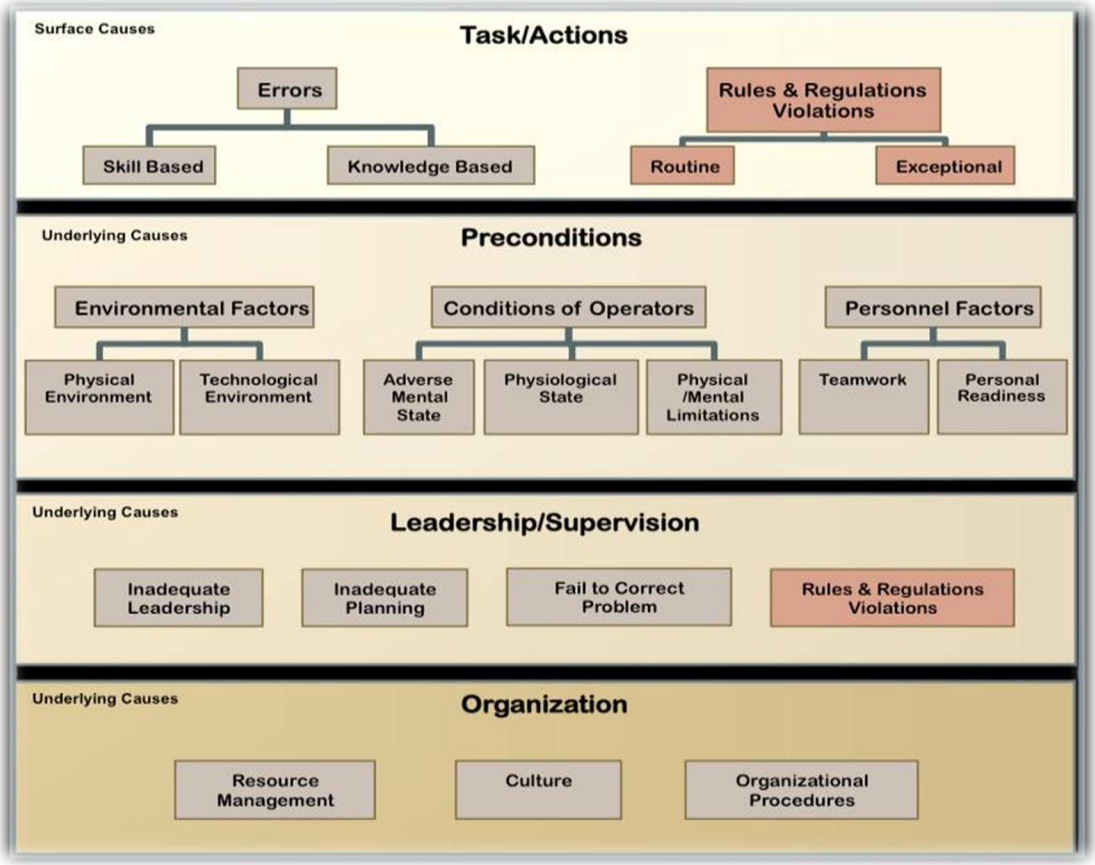

Figure 5. HFACS-bio taxonomy.

Data Collection Process

The data collection took place over a period of 1 week. I recruited six raters in a biopharmaceutical manufacturing company in the United States that produces drug substance products by typical cell culture procedures including upstream and downstream processing. The raters were employees with responsibilities that involved conducting investigations related to human error. In addition, all the raters attended a 2-day seminar on HFACS and passed a test certifying their knowledge in using the taxonomy. The raters also received training in the modified HFACS and the requirements of the study.

No discrepancies emerged from the sample proposed in Chapter 3. The company database containing the incident report investigations was suitable to perform the stratified sampling. Three functional areas or departments of the biopharmaceutical production process sorted the investigations: upstream manufacturing, downstream manufacturing, and services support that included materials processes, maintenance, and engineering. A system specialist conducted a query in the company's incident investigation database for records in which the root cause was human error during a 2-year period from October 2012 to October 2014. I randomly selected the records from each area, 58 records from Upstream, 50 records from Downstream and 53 records from Operational Services for a total of 161 records of incidents.

The investigations were representative of the array of human error investigations present in a typical biopharmaceutical manufacturing organization. The sample included the groups with the majority of the incidents in the main areas of the site. The population was representative from the error investigations that occurred in the biopharmaceutical manufacturing process, as it covered a period of 2 years in which the company was operating at normal capacity under normal production activities.

I assigned each pair of rater the groups of records according to their area of expertise in which they evaluated the incident investigations. The raters used the modified HFACS taxonomy and the definitions provided in Appendix B to evaluate the presence or absence of factors using the information in the incidents reports. The raters used a nominal selection process indicating 0 if the factor was present or 1 if the factor

was not present. I captured the information from the raters in an Excel spreadsheet for both raters per area evaluated (see Appendices C to H).

Results of Study

Descript Statistics

The raters in the study rated no less than 50 incidents for each of the areas in the biopharmaceutical manufacturing process for a total of 161 incidents. The frequency counts for the number of incidents based on organizational area are in Table 2. Similar numbers of incident reports were gathered from upstream (36.0%), downstream (31.1%), and operational services (32.9%).

Table 2

Frequency Counts for Number of Incidents Based on Area

Area	*n*	%
Upstream	58	36.0
Downstream	50	31.1
Operational services	53	32.9

Note. $N = 161$.

The sample size was sufficiently large to comply with the requirements for adequate power and alpha level. As established in Chapter 3, to obtain a power of .95 and the alpha level of .95, the sample needed to be at least 40 incidents per area (Faul et al., 2013; Sim &Wright, 2005). The sample collected in each of the areas exceeded 40, which allowed for the correct power for estimations in the study.

Research Question 1

Research Question 1 was as follows: What is the level of agreement (Cohen's kappa) between the two independent raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes? The related null hypothesis was as follows: The overall Cohen's kappa statistic between the two independent raters was not substantial ($\kappa < .61$) based on the criteria set by Landis and Koch (1977). To answer this question, I calculated kappa statistics for each of the 18 factors and averaged them together. The overall kappa for this study was substantial ($\kappa = .66$; see Table 3) using the criteria set by Landis and Koch (1977). The kappa value of .66 is above .60, which provided support to reject the first null hypothesis.

Research Question 2

Research Question 2 was as follows: What is the difference in the level of agreement (Cohen's kappa) across different areas (operational services, upstream, and downstream) between raters using the revised version of the HFACS taxonomy in biopharmaceutical manufacturing processes? The related null hypothesis was as follows: There are no significant differences between average Cohen's kappa statistics across the operational services, upstream areas, and downstream areas. To test this, I used a one-way ANOVA followed by Scheffe post hoc tests (see Table 4). The overall F statistic was significant ($p = .05$). Scheffe post hoc tests revealed no differences between operations and upstream ($p = .82$) and between upstream and downstream ($p = .16$). However, the mean kappa statistic for operations ($\kappa = .47$) tended ($p = .06$) to be lower

than the mean kappa statistic for downstream (κ = .83). This combination of findings provided support to reject the second null hypothesis (see Table 4).

Table 3

Kappa and Percentage Agreement Statistics Based on Factors and Areas

	All incidents (N = 161)		Operational services (n = 53)		Upstream (n = 58)		Downstream (n = 50)	
Factor	κ	%	κ	%	κ	%	κ	%
Knowledge-based error	.76	92.5	.00	96.2	.48	82.8	1.00	100.0
Skill-based error	.77	91.3	.00	92.5	.62	82.8	1.00	100.0
Routine violation	.60	96.9	-.04	92.5	.85	98.3	1.00	100.0
Exceptional violation	.85	99.4	n/a	100.0	.85	98.3	n/a	100.0
Physical environment	.66	99.4	.66	98.1	n/a	100.0	n/a	100.0
Technological environment	.70	97.5	-.02	96.2	.73	96.6	1.00	100.0
Adverse mental state	.75	93.2	n/a	100.0	.53	82.8	.95	98.0
Physiological state	1.00	100.0	n/a	100.0	n/a	100.0	1.00	100.0
Physical/mental limitations	n/a	100.0	n/a	100.0	n/a	100.0	n/a	100.0
Teamwork	.64	94.4	.66	98.1	.66	89.7	.00	96.0
Personal readiness	.88	96.9	1.00	100.0	.84	94.8	.85	96.0
Inadequate leadership	.79	98.1	.66	98.1	.66	98.3	.88	98.0
Planning	.76	93.8	.85	98.1	.75	89.7	.63	94.0
Failed to correct	.00	99.4	n/a	100.0	.00	98.3	n/a	100.0
Supervisory rules and regulations violations	n/a	100.0	n/a	100.0	n/a	100.0	n/a	100.0
Resource management	.65	97.5	.78	96.2	.00	96.6	n/a	100.0
Culture	.65	93.8	.58	84.9	.73	96.6	n/a	100.0
Processes	.12	93.2	n/a	100.0	.05	81.0	n/a	100.0
Totals	.66	96.5	.47	97.3	.55	93.7	.83	99.0

Note. n/a was given when both raters found no incident to report

Table 4

One Way ANOVA for Kappa and Percentage Agreement Statistics by Area

Statistic and area	*n*	*M*	*SD*	η	*F*	*p*
Kappa [a]				.41	3.27	.05
1. Operations services	11	.47	.40			
2. Upstream	14	.55	.31			
3. Downstream	10	.83	.31			
Percentage agreement [b]				.43	5.87	.005
1. Operations services	18	97.27	3.94			
2. Upstream	18	93.70	6.94			
3. Downstream	18	99.00	1.85			

Note. $N = 161$.
[a] Scheffe post hoc tests: $1 \approx 2$ ($p = .82$); $1 < 3$ ($p = .06$); $2 \approx 3$ ($p = .16$).
[b] Scheffe post hoc tests: $1 > 2$ ($p = .09$); $1 \approx 3$ ($p = .55$); $2 < 3$ ($p = .006$).

Additional Tests

Also in Table 4 was the one-way ANOVA test for the percentage agreement statistics for the three areas. The overall *F* test was significant ($p = .005$). Scheffe post hoc tests found the mean percentage agreement for upstream ($M = 93.70$) was significantly lower ($p = .006$) than the mean percent agreement for downstream ($M = 99.00$). In addition, the mean percent agreement for operations ($M = 97.27$) tended ($p = .09$) to be higher than the mean for the upstream area (see Table 4). Also, I calculated only 35 out of a possible 54 kappa scores (18 factors × 3 areas) because SPSS would not calculate a kappa score when both sets of raters found no incident to report.

The paired *t* tests and Pearson correlations between the four tiers and the overall scores are in Table 5. I calculated the tier score by summing together the number of incidents observed for the tier's individual factors. Out of a possible 18 factor points, the overall mean number of incidents for the first set of raters was $M = 1.79$ and the mean

number of incidents for the second set of raters was $M = 1.83$. This difference was not significant ($p = .44$). The interrater correlation between the two scores was $r = .75$ ($p < .001$). Three of four other correlations were all above $r > .70$. Paired t tests also indicated that three of the four tier scores were not significantly different between the two sets of raters. However, in the leadership/supervision tier (possible 4 points), the first raters reported significantly more incidents ($M = 0.23$ vs. $M = 0.18$; $p = .03$).

Table 5

Paired t Tests and Pearson Correlations Comparing Tier Incident Scores for Raters

Tier and rater set	Number of factors	*M*	*SD*	*r*	*t*	*p*
Task/actions	4			.71	1.42	.16
First		1.00	0.11			
Second		1.01	0.16			
Preconditions	7			.73	1.14	.26
First		0.40	0.55			
Second		0.44	0.58			
Leadership/supervision	4			.74	2.16	.03
First		0.23	0.42			
Second		0.18	0.39			
Organizational influence	3			.46	0.90	.37
First		0.16	0.40			
Second		0.19	0.44			
Overall total score	18			.75	0.78	.44
First		1.79	0.71			
Second		1.83	0.72			

Note. $N = 161$. r = Pearson correlation. *M = errors per incident.*

The number and percentage of reported incidents for each factor for the two sets of raters are in Table 6. The two sets of raters identified skill-based errors most frequently (72.0% and 78.3%) as similar numbers of incidents observed for the other

factors (see Table 6). The factors supervisor rules and regulations, rules and regulations, supervisor failed to correct problem, and physical/ mental limitations were the lowest factors identified or the raters did not identify them in any of the incident reports.

Table 6

Number and Percentage of Incidents for Each Factor for the Two Sets of Raters

First raters			Second raters		
Factor	*n*	%	Factor	*n*	%
Skill-based error	116	72.0	Skill-based error	126	78.3
Knowledge-based error	34	21.1	Adverse mental state	31	19.3
Inadequate planning	27	16.8	Knowledge-based error	28	17.4
Adverse mental state	22	13.7	Inadequate planning	23	14.3
Personal readiness	18	11.3	Culture	19	11.8
Teamwork	14	8.7	Personal readiness	18	11.2
Culture	13	8.1	Teamwork	13	8.1
Inadequate leadership	9	5.6	Technological environment	7	4.3
Organizational procedures	7	4.3	Resource management	6	3.7
Technological environment	7	4.3	Organizational procedures	6	3.7
Routine violation	7	4.3	Routine violation	6	3.7
Resource management	6	3.7	Inadequate leadership	6	3.7
Exceptional violation	4	2.5	Exceptional violation	3	1.9
Physical environment	2	1.2	Physiological state	2	1.2
Physiological state	2	1.2	Physical environment	1	0.6
Failed to correct	1	0.6	Supervisor rules and regulations	0	0.0
Supervisor rules and regulations	0	0.0	Failed to correct	0	0.0
Physical/mental limitations	0	0.0	Physical/mental limitations	0	0.0

Note. $N = 161$.

Summary

In summary, this study included data from 161 incidents to examine the utility of the HFACS to the investigation of human error and deviations in the biopharmaceutical

industry to identify the factors that lead to human error in biopharmaceutical manufacturing operations by assessing the interrater reliability of a modified taxonomy. Hypothesis 1, which I used to determine the overall kappa statistic of two independent raters using the modified HFACS taxonomy, received support from results that showed a substantial overall kappa with a result of $\kappa = .66$ (see Table 3). Hypothesis 2, which I used to examine the difference among operational services, upstream manufacturing, and downstream manufacturing, also received support from the one-sided ANOVA (see Table 4). The one-way ANOVA and Scheffe post hoc test for Cohen's kappa, as well as the percentage agreement statistics for the three areas, showed a significant F value ($p = .005$). The results revealed that there was no significance difference between raters when using the modified taxonomy. Furthermore, there was no significance difference among the incident investigations from the different areas of the manufacturing processes of the biopharmaceuticals evaluated. Therefore, the interrater reliability of the modified HFACS taxonomy was adequate for the investigations examined in the study. A comparison of the study finding to the literature, conclusions and implications for practice and social change, and a series of recommendations are in Chapter 5.

Chapter 5: Discussion, Conclusions, and Recommendations

The purpose of this quantitative interrater reliability study was to determine the utility of the HFACS taxonomy for conducting human error investigations in biopharmaceutical manufacturing processes. Human errors are a recognized problem in the biopharmaceutical industry due to the detrimental implications to products, resources, and people. Although researchers have conducted studies demonstrating the effectiveness of the HFACS for error investigations in the aviation industry as well as other domains such as transportation, mining, and health care operations, minimal research exists on using the taxonomy in the biopharmaceutical industry. This study led to additional information in the area of using the HFACS in the biopharmaceutical industry by answering questions that contributed to addressing the literature gap.

This study included two research questions and an objective to assess the interrater reliability of a modified version of the HFACS for biopharmaceutical manufacturing process investigations. I used Research Question 1 to evaluate the reliability of two individual raters using the modified taxonomy to examine incident investigations related to human errors in three areas of a biopharmaceutical manufacturing company. I used Research Question 2 to evaluate the difference among the obtained interrater reliabilities. Statistical analysis on the 161 incidents evaluated by the raters led to me accepting the hypotheses.

A detailed discussion of the results presented in Chapter 4 with conclusions and recommendations appears in Chapter 5. The analysis includes a comparison of the findings with the current literature and an interpretation of significant findings followed

by the limitations of the study, recommendations for future research, and implications for social change. Recommendations for members of the biopharmaceutical community, including manufacturing and regulatory leaders, also appear in the chapter.

Interpretation of Findings

The findings in the study include information that extends the knowledge about using human factors taxonomies such as the HFACS for investigating human errors in other domains such as the manufacturing processes of biopharmaceutical products. Those results aligned with studies in which the researchers demonstrated the applicability of the HFACS in various domains for the investigation of errors (Berry et al., 2010; ElBardissi et al,, 2007). Thus, the results obtained in this study supported using the modified taxonomy in the biopharmaceutical industry. I will show how the specific results obtained in relation to each of the research questions compare with the literature studies.

Research Question 1

To answer Research Question 1, six independent raters divided in three pairs based on the area of expertise, evaluated a sample of incident reports from different areas in a biopharmaceutical manufacturing process using the modified HFACS taxonomy to calculate the level of agreement (Cohen's kappa) between them. The results obtained from the statistical analysis rejected the null hypothesis, as the overall Cohen's kappa statistic between the two independent raters was substantial ($\kappa > .61$). The overall kappa for the 18 factors was substantial ($\kappa = .66$).

Overall Cohen's kappa values across the tier and factors were all positive, with the exception of the areas in which all the raters fully agreed on the absence of the factor, meaning that agreement exceeded chance at the 95% confidence level. Therefore, the estimated kappa values ranged from substantial to perfect agreement at the individual area level, as well as from moderate to perfect at the overall kappa level. These results were in general agreement with previous studies of interrater reliability for error taxonomies.

Previous studies positively assessed the reliability of the HFACS taxonomy with the use of interrater reliability and the measurement of kappa statistics. As part of their HFACS development work, Wiegmann and Shappell (2003) conducted interrater reliability studies using Cohen's kappa statistics resulting in substantial results (.60 to .74) according to Landis and Koch (1977). Furthermore, researchers in recent interrater reliability studies obtained similar results like this study where Cohen's kappa showed agreement that exceeded chance at the 95% confidence level with values from .54 to 1.00 (Ergai, 2013). However, as previously discussed in the review of literature, not all researchers are in agreement with the high interrater reliability demonstrated on the use of the HFACS.

Other researchers have questioned the validity of the studies of interrater reliability of the HFACS taxonomy. According to Olsen and Shorrock (2010), low agreement using HFACS-type categories showed lack of consistency, which indicated the taxonomy was unreliable. Furthermore, Olson and Sharrock challenged the quality of the execution and the methodology of the studies, mostly due to the lack of independence of

the coders. The discrepancy from the results obtained in this study may be due to the quality of the information and the experience of the personnel involved in the investigation process. In this study, the coders were independent, and there was no direct relationship or bias regarding the information documented in the incident reports. Although there is substantial reliability information around the HFACS taxonomy in the aviation domain, the information available in other industries remains limited. Nevertheless, the information provided in this study on using the HFACS included significant knowledge to improve the quality of the human error investigations process in the biopharmaceutical industry, particularly the information from the different functional areas of the operations and evaluated using Research Question 2.

Research Question 2

For Research Question 2, the study provided data on the difference among operational areas of the site. Especially notable was the level of agreement present when comparing the agreement among raters from the areas of upstream manufacturing, downstream manufacturing, and operational services. The analysis of the data demonstrated that I could reject the null hypothesis, as the results showed no statistically significant differences across the areas.

Examining the specific variations among the areas revealed some of the values were close or tended to significance based on the Sheffe post hoc test. For instance, although the post hoc test revealed no differences between operations and upstream (p = .82) and between upstream and downstream (p = .16), the mean p value for the kappa statistic for operation services is considered to be *tended* (p = .06) as it is too close to be

statistically significant ($p < .05$). However, the values supported rejecting the second null hypothesis, as there was a statistically significant difference among the areas.

These results are in agreement with previous published results in interrater reliability studies. For instance, a study conducted by Li and Harris (2005) to evaluate the interrater reliability in aviation accidents using the HFACS showed Cohen kappa results between .44 and .83, which indicated moderate to satisfactory agreement and showed significant statistical variation. However, in the same study, Li and Harris (2005) found that the percentage agreement was higher than demonstrated by the kappa and showed acceptable reliability. Olsen (2011) reported similar results when evaluating reliability among groups, and the percentage agreement was a better indication of the reliability of the use of the taxonomy among functional groups.

I analyzed the one-way ANOVA results for the percentage agreement statistics for the three areas to gain a deeper knowledge of the relations among the raters. Some of the individual areas had no kappa values because the raters agreed that there were no factors. For instance, in Table 3, the kappa value for physical/mental limitations appeared as n/a, even though there was a 100% agreement among all the six raters. Thus, only 35 out of the 54 expected kappa scores existed.

The percentage agreement statistical analysis provides an additional assurance or perspective than just the kappa value when evaluating the intererater results among areas. For instance, from all the areas in the factors assessment, the percentage agreement among raters fluctuated between 94% and 100%. This result compared favorably with other interrater reliability results from studies conducted using the taxonomy where the

percentage agreement was between 53% and 99% for all the factors (Ergai, 2013; O'Connor, Walliser, et al., 2010; Olsen & Shorrock, 2010; Olsen, 2011). I performed the other statistical tests to evaluate Research Question 2 using percentage agreement among raters.

I conducted statistical analysis of percentage agreement among the each of the pairs of raters for the biopharmaceutical functional areas and therefore rejected the null hypothesis, which validated the reliability of the taxonomy. For the null hypothesis, the overall F test was significant ($p = .005$), and the Scheffe post hoc tests revealed the mean percentage agreement among the areas is not statistically different ($p > .05$). The results aligned with the reliability studies previously conducted by other researchers confirming the validity of the HFACS taxonomy (Ergai, 2013). Contrasting results indicated the level of agreement can vary when evaluating the individual factors and the tiers. For instance, Olsen and Shorrock, (2010) identified lower percentage agreement at the individual factor level and higher percentage agreement at the HFACS four tiers. Additional testing involved evaluating the result considering the tier levels.

Additional Tests

The results of the scores when analyzing the interrater results at the tier level of the HFACS taxonomy appeared in Table 5. The results showed the t tests and Pearson correlations between the tier scores. The results confirmed that there were no significant differences ($p > 0.5$) among the pair of raters at the overall level. Each rater identified an average of almost two factors when evaluating the events. The first set of raters identified 1.79 factors per incident while the second set of raters identified 1.83 factors

per incident. The reliability study demonstrated that there was no statistically significant difference (p = .44) for the raters based on the results. Therefore, based on the results it is evident that there are at least two factors from the taxonomy present in the incidents evaluated. Although this part was out of the scope of this study, I observed that the data identified some potential elements of causality in the incidents.

The theoretical framework of the HFACS is the Swiss cheese framework. According to the Swiss cheese theory, a combination of underlying factors or causal factors comprises the root cause of error events (Reason, 1990, 2008). Literature supports that those factors exist in combination during the error events (Berry et al., 2010; ElBardissi et al., 2007). Although I did not evaluate the data of the various factors included in the incidents for causality, I will not discard the possibility that raters observed the phenomenon identified in other studies as the combination of multiple causal factors in the incidents evaluated. This information is a potential topic for future research, as discussed later in this chapter.

As an additional test, I also evaluated the number and percentage of each factor identified by the raters. For all the six raters the top four factors most commonly identified by the raters were skill-based errors, knowledge-based errors, adverse mental state, and inadequate planning. The two most frequently identified factors were from the task/action tier of the HFACS taxonomy. The most common factors identified were in agreement with the data obtained from the literature review. For instance, in the majority of the incidents evaluated in the studies, the top factors identified were the error factors *skill based* and *knowledge/decision based* (Berry et al., 2010; ElBardissi et al., 2007;

Ergai, 2013; O'Connor, Walliser, et al., 2010; Olsen, 2011; Olsen & Shorrock, 2010). It was also relevant that the other top factors were from different tiers also associated with the elements of causality.

As indicated before, researchers use the HFACS taxonomy to investigate errors by identifying factors in tiers that can interact with each other or prevail in the systems as underlying causes. Extensive literature exists to support the use of the HFACS in the aviation and transportation domains (Berry et al., 2010). More researchers have been advancing the use of the HFACS taxonomy outside of the aviation and transportation areas toward health care settings such as operating rooms (Catchpole et al., 2007; Diller et al., 2014; ElBardissi et al., 2007; Wiegmann & Dunn, 2010). Those researchers indicated that it is necessary to identify the underlying causes of errors to identify the effective corrective actions. Although limited research still exists, the HFACS allows researchers to identify interactions among causal factors that can support the identification of adequate corrective actions.

In summary, the findings of this study supported the two research questions regarding the adequacy of a modified HFACS as a tool to support human error investigations in the biopharmaceutical industry. I evaluated interrater reliability by analyzing the variability between two independent raters as well as by verifying the statistical variability among incidents in different working areas of a biopharmaceutical manufacturing facility. Although there were no published studies in the biopharmaceutical manufacturing domain, the results of the reliability studies compared satisfactorily with similar reliability studies conducted in other industries with the

HFACS taxonomy. The HFACS is an acceptable tool to facilitate human error investigations through evaluating and identifying human factors as underlying causes in multiple layers of operations settings. The theoretical foundation on the Swiss cheese framework of causal factors aligned perfectly with the mission of identifying the underlying causes of human errors. The results of the study confirmed general research in the area supporting the adaptability and usability of the HFACS to different domains. Based on the result of the study, the HFACS taxonomy can be considered applicable to the biopharmaceutical manufacturing industry considering the limitations of the study.

Limitations of the Study

I identified some limitations during this study. The main limitation was that the available information of the incidents was not originally collected using the modified HFACS taxonomy. For that reason, some of the factors identified as not present could have been because no one collected or considered the information during the initial investigations and not because there were none present. That limitation existed in similar studies conducted in other domains in which researchers used the analysis of previous incidents to evaluate the HFACS taxonomy (Berry et al., 2010). However, the limitation did not adversely affect the validity of the study because I was able to achieve sufficient statistical robustness.

Another limitation of the study is the use of Cohen kappa as the main statistical tool used to evaluate the interrater variability of the independent raters. The lack of kappa calculation in some factors could also be due to the limitation of the information available in the incident documents. However, when all the six raters agreed on the

absence of a particular factor, the kappa calculation was not possible. Although the overall Cohen's kappa statistic for interrater reliability was an acceptable and recognized statistic for these studies, additional statistical analysis such as the percentage agreement is necessary to complement the study (Hanneman et al., 2012). In this study, the percentage agreement served as an additional test to compensate for the limitations of the kappa and to maintain a correct level of validity. In addition, the overall kappa was available for the analysis, which mitigated the statistical limitation.

Another limitation previously identified was the raters' lack of experience with the HFACS taxonomy. This is a common limitation identified in the literature and represents a concern regarding the validity of previous reliability studies on the HFACS taxonomy (Olsen, 2011, 2013). The detailed training conducted by industry experts in the HFACS taxonomy, and corroborating knowledge with an independent certification test provided by the expert, mitigated that limitation.

The final limitation of the study was that it included a single biopharmaceutical manufacturing facility, which limited the generalizations of the study to that type of manufacturing process. The facility selected for the study could be representative of a large-volume manufacturer of biopharmaceutical drug substances using typical cell culture processes in an upstream and downstream design regulated by the general government global pharmaceutical authorities. Conducting future research in accordance with the recommendations may further mitigate many of the limitations of the study.

Recommendations

The findings of this study included the beginning of a new methodology for advancing human error investigations in the biopharmaceutical manufacturing industry. However, as indicated in the limitations, further research is necessary to continue closing the gaps and the unknowns in the area of human factors and the use of HFACS in the industry. Further research is necessary to expand knowledge on the reliability of the modified HFACS taxonomy after conducting incident investigations on real-time issues. The research can also expand to determining the ease of use or practicality in such actual incident investigations.

Therefore, further research is necessary to determine the reliability of the modified HFACS taxonomy when raters evaluate an actual event. In a similar manner, a researcher can evaluate the interrater reliability of events investigated using the modified HFACS. The study can also involve comparing the results of this study or the reliability with other industries using HFACS in a similar fashion. The limitations also indicated the lack of experience with the HFACS taxonomy.

After implementing the modified HFACS to conduct investigations, raters will develop knowledge and skills in the area. Future research could reveal how the interrater reliability of the HFACS changes with additional practice and experience. Future researchers can compare the difference between experienced and inexperienced investigators to examine changes in reliability when using incidents created with the HFACS taxonomy.

I established that the current process for conducting error investigations in the biopharmaceutical industry is lacking depth considering the underlying causes provided by the HFACS taxonomy. Researchers can measure the improvement of the investigational process after implementing the HFACS (Berry et al., 2010). Researchers can also determine the prevalence of factors in biopharmaceutical manufacturing processes, including what type of association can be determined from the causal factors in the biopharmaceutical industry and other industries. The comparison and contrast of factors present in investigations in biopharmaceutical processes can be evaluated among different geographical regions, typology of products as well as manufacturing processes. Future researchers can study and compare the relationships among the factors in the various HFACS tiers among different groups of organizations.

Finally, if better information and higher quality investigations result from using the HFACS, it is important to evaluate the effectiveness of that process. Researchers can evaluate the effectiveness of the investigations process after implementing the HFACS. That effectiveness can answer the question regarding the quality of the investigations as measured by regulatory agencies. Researchers can also measure the quality of the investigation process after HFACS implementation by the effectiveness of the corrective actions. In addition, investigators can use their experience with the HFACS to determine the level of quality of the process, ease of use, and level of employee satisfaction.

Implications

In this study, I identified the reliability of the HFACS as an alternative to improve the quality of the levels of error investigations in the biopharmaceutical industry. Human

error investigations are still lacking, as the use of root cause analysis is neither standardized nor reliable between organizations, the main focus is on who to blame for the error, and no nomenclature allows the analysis of recurring errors across companies (Clarke, 2009; Poska, 2010). The inability of controlling human errors has detrimental effects in the business, regulatory bodies, and society. The implications of this study can help address the adverse effects of human error by providing an alternative to improve understanding in the area and establish better corrective actions to reduce such errors.

Positive Social Change

Health care costs are a social problem directly affected by the cost and availability of medicines. Human errors in biopharmaceutical manufacturing organizations are a problem with a direct impact to costs, production reliability, and safety of industrial products (Glavin, 2010). Part of the social responsibility of companies is to improve the condition of their employees, their customers, and their environment. Errors have the potential to create a negative impact on all the areas that constitute a company's responsibility.

The findings of this study may serve as a tool for leaders of biotechnology manufacturing companies to reduce and mitigate the adverse effects of human error while improving the effectiveness of their processes. Implementing HFACS can provide an improvement of the conditions of the operators by allowing them to prevent manufacturing incidents and safety accidents. Fewer accidents should reduce labor costs of the organizations and the social impact of disabilities. A better understanding of the human causal factors of errors using the HFACS can reduce errors that delay new

products needed to fulfill unmet medical needs, prevent the loss of products that can create drug shortages, and prevent losses that increase the cost of medicines.

Methodological Implications

Given the findings from the review of the literature, and given what I found in this study, the HFACS is comprehensive and reliable for conducting investigations of human errors in the biopharmaceutical manufacturing industry. Although the findings in the majority of the reviewed literature supported using HFACS for investigations of causal factors that generate errors resulting in accidents, other research has revealed support for use in operational settings (Diller et al., 2014). However, to maintain the reliability of using the error taxonomy and the trustworthiness of future studies, it is important to use adequately trained, unbiased, and experienced individuals to conduct error investigations (Olsen, 2011, 2013). Evaluating human factors, especially involving individuals, is a sensitive issue.

Recommendations for Practice

The results obtained in this study provided an alternative for improving the current process of conducting human error investigations in the biopharmaceutical manufacturing setting. Researchers could use the modified HFACS used in this study to increase the level of such investigations while identifying better the underlying human factor causes that can drive better corrective and mitigating actions. However, using HFACS is new for the pharmaceutical industry and may face resistance.

Error investigations in the biopharmaceutical industry have involved using tools focused on process deficiencies. The bases of conventional investigation processes in the

pharmaceutical industry are process optimization tools and problem-solving techniques without considering human factors (McCormick & Wylie-McVay, 2012; Myszewski, 2010, 2012). However, humans do not behave like machines and the same factors do not affect them. Therefore, it is important to differentiate process deviation investigations from human factors investigations.

The leaders of regulatory bodies of the biopharmaceutical industry are aware of the impact of human errors in the process of drug manufacturing. Current regulations require reviewing records for the presence of errors as well as for executing investigations capable of identifying root cause and effective corrective actions (Rodriguez-Perez, 2011). Furthermore, leaders in regulatory agencies such as the FDA recognized the negative impact of human errors in manufacturing process deviations (Friedman et al., 2011). However, no clear regulatory requirements include human factors analysis as part of the error deviation investigative process.

Although leaders of regulatory bodies recognize aviation human factors techniques as effective, regulatory activity in the area is passive or indirect. For instance, leaders of biopharmaceutical regulatory bodies in Europe commissioned a study to evaluate if current regulations prevented using human factor tools for investigating error (Konstantinos et al., 2011). Furthermore, Konstantinos et al. (2011) indicated that the regulations are not in conflict with using human factors tools, and the biopharmaceutical manufacturers will benefit from using human factors in their investigations and corrective actions development. However, there are no clear requirements from any regulatory body on how to use human factor analysis in the investigative process of error deviations.

The HFACS taxonomy may be concerning to industry leaders because it involves evaluating the operators, leadership/supervisors, and organizational practices to identify latent conditions. This is different from the current practice in the industry, which involves only the operator executing the functions and uses retraining as the main corrective action (Poska, 2010). To establish a suitable process to facilitate the use of the HFACS in investigations, the company's leadership needs to create a just culture that fosters open communication in a blame-free environment.

Creating an open culture in any health care environment would involve a paradigm shift for leadership. A just culture is not the same for all health professionals, as it represents a predicament regarding the accountability of errors (Dekker & Nice, 2013). The resulting environment will prevent the open communication of errors with concerns about negative or adverse implications for stakeholders, including staff, regulatory bodies, and the public. For that reason, leaders of biopharmaceutical industries need to collaborate with regulatory bodies to implement the practice of human factor analysis tools such as the HFACS in investigations of errors in a just culture and an open environment that fosters the well-being of all stakeholders.

Conclusions

Every working place in which humans execute functions and operations has a high chance for errors. In the biopharmaceutical manufacturing industry, many individuals conduct critical and complex operations in which the opportunities for and occurrence of human errors are prevalent. The problem is that the process used for

conducting human error investigations in the biopharmaceutical industry is deficient and does not include human factors analysis to understand the underlying causes of errors.

Researchers developed and successfully used the HFACS taxonomy in the aviation industry to investigate accidents considering causal factors. Researchers in other industries used the information gained from using the HFACS in aviation and deployed its use in their accident investigations successfully. Although the literature is limited, investigators in the field of health care have been applying the HFACS to investigate the occurrence of errors in their operations with promising results (Diller et al., 2014; ElBardissi et al., 2007). Previous researchers identified a gap in the investigative process in the pharmaceutical and the biopharmaceutical industries regarding investigations and root cause analysis of errors in their operations and the regulatory applicability of aviation tools for that effect (Konstantinos et al., 2011). However, the literature indicated the lack of application of HFACS techniques in biopharmaceutical manufacturing.

In this quantitative interrater reliability study, I examined the utility of a modified HFACS for human error investigations in the biopharmaceutical industry. I designed the study to answer two research questions centered on determining the level of agreement between independent raters using a modified HFACS taxonomy, as well as the difference in the level of agreement across different areas of biopharmaceutical manufacturing processes. Raters examined a stratified sample of 161 incident investigations encompassing a 2-year period in a fully crossed experimental study.

I analyzed the interrater reliability as well as the relationships among the reliabilities among areas of a typical biopharmaceutical manufacturing company of drug

substance material (operational services, upstream manufacturing, downstream manufacturing) to calculate the overall Cohen's kappa, percentage agreement, and one-way ANOVA test with Scheffe post hoc tests. Results obtained in the study showed acceptance of the reliability of the modified HFACS taxonomy when used in the investigations of biopharmaceutical manufacturing operations. The results indicated that there was no statistical difference ($p < .05$) with substantial Cohen's kappa values of .66. The results of this study were in agreement with previous HFACS interrater reliability studies in the literature. In addition, the main factor of knowledge-based and skill-based errors emerged as the most prevalent in the investigations, which aligned favorably with the literature in the area.

The findings of this study indicated the HFACS can help biopharmaceutical manufacturers to decrease human errors and improve the safety and reliability of their processes with better investigations and root cause analysis. However, using the HFACS for conducting investigations represents a paradigm change for leaders and regulators in the biopharmaceutical industry. Human factors analysis using the HFACS includes an evaluation of underlying causes at the leadership and organizational level that differs from the current operator/process improvement mode of investigations. Industry practitioners and leadership should collaborate with leaders of regulatory agencies to create a culture of openness and reporting that will facilitate the introduction of investigative tools such as the HFACS, which will result in better interventions for human error reductions. The result could be a more reliable and efficient biopharmaceutical manufacturing industry.

Such reliability and efficiency results from the implementation of the HFACS can have positive social implications. Fewer human errors can promote better management of manufacturing costs and increased reliability. The public expects that manufacturers of biopharmaceutical products, in collaboration with regulatory authorities, are capable of consistently providing affordable, safe, and effective products. The public does not expect defective and ineffective products with low quality. As previously discussed, human errors have a direct adverse impact on the cost and quality characteristic of biopharmaceutical products. According to the findings of this study, the implementation of the HFACS can increase the understanding and prevention of such errors by diminishing the adverse consequences of resource waste that can help support the development of new drugs to address the unmet medical needs of society.

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Appendix A: Letter Soliciting Participation in Research Study

Day Month, 2014

Dear BioPhorum Member,

The purpose of this letter is to solicit your expert input in a research study. I am a doctoral candidate at Walden University in the Management Program specializing in Leadership and Organizational Change. My dissertation is titled Inter-rater Reliability Study of the Human Factors Analysis and Classification System for Human Error Investigations in Biopharmaceutical Manufacturing.

The results of this study could provide information that increases understanding of factors that affect human errors in the biopharmaceutical operations. Moreover, the results will provide with additional tools to improve the investigations process in that industry. As part of my study I am requesting an assessment of a modified taxonomy that includes causal factors of errors. The modified taxonomy presented is a derivative of the human factors analysis and classification systems (HFACS) extensively used in the aviation industry for accident investigations. I am asking that you provide feedback about how comprehensive is the factors identified in the proposed taxonomy to aid in the identifications of root causes of incidents associated with human errors in the biopharmaceutical industry.

The information provides is strictly anonymous and will only be used to assess further changes needed to the proposed HFACS taxonomy derivative. Neither the participants' nor the organization's name will be revealed in my dissertation.

The results of this research will be made available to all participating organizations through the BioPhorum group upon completion of my dissertation. I will appreciate your support in considering the evaluation of the forms used in my study. Should you have any questions, please e-mail me.

Thank you in advance for your consideration.

Sincerely,

Roberto Cintron
Doctoral Candidate Walden University
Management, Leadership and Organizational Change

Appendix B: The HFACS Biopharmaceutical Derivative

Category	Causal factors	Definition	Reference
		Task/Actions	
	__ Decision	Conscious mental judgment action. Knowledge, experience and awareness.	Wiegmann & Shappell, 2003 Hsiao et al., 2013a, 2013b
	__ Skill-base	Actions were made without conscious thinking (Automatic)	
	__ Routine	Habitual violations tolerated by leaders	Patterson & Shappell, 2010
	__ Exceptional	Isolated departures not condoned by management	
		Preconditions	
Environmental Factors	__ Physical environment	Operational setting and the ambient conditions	Walker et al., 2011
	__ Technological environment	Design of equipment, controls, and automation	Schröder-Hinrichs et al., 2011
Conditions of operators	__ Adverse mental state	Conditions affecting execution (fatigue, demotivation)	Wiegmann & Shappell, 2003
	__ Psychological state	Acute medical and/or physiological conditions (illness)	
	__ Physical/Mental Limitations	Disabilities such as poor vision or lack of strength	
Personnel Factors	__ Teamwork	Communication, coordination, and teamwork issues	Patterson & Shappell, 2010
	__ Personal Readiness	Inadequate training, lack of rest	Wiegmann & Shappell, 2003
		Leadership/Supervision	
	__ Inadequate supervision	Oversight of personnel and resources, professional guidance, and tactical leadership	Hsiao et al., 2013a
	__ Planned activities	Management and assignment of work including operator pairing and operational activities	Hsiao et al., 2013a
	__ Failed to correct the problem	When deficiencies are "known" to members of leadership yet are allowed to continue uncorrected.	Patterson & Shappell, 2010
	__ Rules & regulations violations	Disregard for rules, regulations, SOP's by leaders	Patterson & Shappell, 2010
		Organizational Influences	
	__ Resource management	Management of human, monetary, and equipment resources necessary for operations	Patterson & Shappell, 2010
	__ Climate	Organizational direction including policies, leadership structure, and culture	Berry et al., 2010
	__ Organizational processes	Formal processes by which the vision of an organization is executed	Wiegmann & Shappell, 2003

Note. This document was created by combining the elements from the sources included in the references column to form the HFACS Biopharmaceutical derivative.

Appendix C: Operational Services Rater 1 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
6	0	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
7	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
8	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
24	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
38	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

40	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
41	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
42	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
43	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
44	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
46	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
48	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
51	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
52	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
53	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Appendix D: Operational Services Rater 2 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Supervisor Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	1	0
4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
6	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0
7	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0
8	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
14	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	0
15	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
18	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
24	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
26	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
27	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
34	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
38	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
39	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0

40	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
41	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0
42	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
43	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
44	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
46	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
47	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
48	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
49	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0
51	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
52	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
53	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

Appendix E: Upstream Rater 1 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Supervisor Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
4	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
5	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
6	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
7	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
8	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
9	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
10	1	0	0	0	0	0	1	0	0	0		0	0	0	0	0	0	0
11	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
12	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
13	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
14	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
15	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
16	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
17	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
18	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
19	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
20	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
21	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
22	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
23	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
24	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
25	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
26	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
27	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
28	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
29	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
32	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
33	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
34	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
35	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
36	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
37	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
38	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
39	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

40	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
41	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
42	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
43	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
44	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
46	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
47	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
48	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
49	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0
51	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
52	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
53	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
54	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
55	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
56	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
57	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
58	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

Appendix F: Upstream Rater 2 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
2	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
4	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
5	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
6	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
7	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
8	0	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
9	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
10	1	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
13	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
14	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
15	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
16	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
17	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
18	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
19	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
21	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
22	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
23	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
24	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
25	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
26	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
27	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
28	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
29	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
32	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
33	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
34	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0
35	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
36	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
37	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
38	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

39	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
40	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
41	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
42	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
43	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
44	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
46	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
47	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
48	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
49	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	1	0	0	1	0	0	0	0	0	1	0	0	0	0	0
51	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
52	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
53	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
54	0	1	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
55	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
56	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
57	0	1	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
58	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0

Appendix G: Downstream Rater 1 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
6	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
7	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
8	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
9	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
10	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
15	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
16	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
17	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
18	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
19	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
21	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
24	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
26	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
27	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
28	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

34	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
35	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
39	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
43	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
44	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
46	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
47	0	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
48	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
49	1	0	0	0	0	0	0	1	0	1	0	1	0	0	0	0	0	0
50	0	1	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0

Appendix H: Downstream Rater 2 Data

Record Number	Knowledge-Based Error	Skill-Based Error	Routine Violation	Exceptional Violation	Physical Environment	Technological Environment	Adverse Mental State	Physiological State	Physical/Mental Limitations	Teamwork	Personal Readiness	Inadequate Leadership	Planning	Failed to Correct	Rules and Regulations Violations	Resource Management	Culture	Processes
1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
6	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
7	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
8	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
9	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
11	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
15	1	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0
16	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
17	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
18	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
19	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
21	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
24	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25	1	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0
26	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
27	0	1	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0
28	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
29	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
30	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
31	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
32	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

34	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
36	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
37	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38	0	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
39	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
40	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
41	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
42	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
43	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
44	0	1	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
45	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
46	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
47	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
49	1	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0
50	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0

Curriculum Vitae

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Education

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Work Experience

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Johnson & Johnson Pharmaceuticals Companies
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Centocor Inc., Malvern PA 2003 – 2007
Johnson & Johnson Pharmaceutical Companies
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Ortho Biologics LLC, Manati PR 1999 – 2003
A Johnson & Johnson biotechnological company
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West Pharmaceutical Services, Canovanas PR 1998 – 1999
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Novartis Consumer Health, Humacao PR 1992 – 1998
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Warner Lambert Inc., Fajardo PR 1990 – 1992
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Beckman Instruments, Naguabo PR 1985 – 1990
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