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Assuring highly potent active ingredient safety: the SafeBridge certification program

INTRODUCTION

Drug innovators, collaborators, licensing partners and the myriad of third parties who handle active pharmaceutical ingredients (APIs) need to take notice when the APIs they are handling have the following properties – clinical doses less than 10 milligrams causing pharmacological or toxic effects in patients or if low doses (less than 1 mg/kg/day) in laboratory animals may potentially be “-genic” (i.e., they are mutagenic, teratogenic, carcinogenic or are reproductive or developmental toxicants). These are the definitions or “red flags” for a “potent” compound which requires containment and controls (“hardware”) and programs and practices (“software”) to minimize worker and environmental exposure. More and more drugs meet these potent compound criteria. Management systems need to be developed by big and small API manufacturing, finished product manufacturing and R&D locations to implement the hardware and software that go beyond traditional approaches to safe handling of “typical” chemicals. Approaches to assuring compliance in pharmaceutical R&D and manufacturing workplaces are typically through audit or assessment of cGMP or GLP compliance. Potent compound safety requires the same degree of assessment as the risks of inadequate containment, lack of exposure controls and improper handling of the API can be significant (for example, causing an adverse health effect in workers handling the drug or impeding speed to market).

SafeBridge Consultants, Inc. of Mountain View, California has created and implemented a metric that determines the capability of a pharmaceutical or fine chemical company to meet current industry practices in the health and safety aspects of potent pharmaceutical manufacture and R&D. The process is called the SafeBridge Certification program and it assesses the strengths and weaknesses of the systems, programs and facilities in the area of worker protection. The outcome of the process alerts the manufacturer’s management of areas that may not meet current pharmaceutical industry standards or practices. The process utilizes a sixty-point assessment criteria and scoring system developed by SafeBridge health and safety professionals for this purpose. This process can be used as either a “gap assessment” tool for company self-evaluation or as a means to certify, through independent objective review, that the company is

competent in potent compound safety for the purpose of marketing their manufacturing capability to outside parties and potential clients.

Specific regulations for occupational exposure prevention to highly potent pharmaceutical materials do not exist and the industry is largely self-regulated regarding pharmaceutical product exposure control.

Common approaches have been developed by the large pharmaceutical companies to meet their ethical obligations and the “general duty” regulations of providing a safe and healthful working environment. Therefore the Certification process is not a strict regulatory audit, rather the assessment is designed to determine the gaps that companies seeking contract pharmaceutical product development and clinical and commercial manufacturing could identify when evaluating the capabilities of a company in potent compound safety.

THE CERTIFICATION PROCESS – PHASE 1

The process involves a pre-visit questionnaire issued to the company regarding the nature of the facility, processes and programs in environmental health and safety (EH&S) that may affect manufacturing. The company will provide SafeBridge with responses to the pre-visit questionnaire and, if available, the following information:

- Engineering design drawings of the layout of the facility;
- An equipment inventory;
- A chemical inventory or, at a minimum, a list of active pharmaceutical ingredients (APIs) used at the facility;
- Any descriptions of existing exposure control technology;
- Process flow diagrams for each typical process employed;
- Control Matrix (or control banding system); and
- Relevant Standard Operating procedures (SOPs).

PHASE 2 - ON-SITE ASSESSMENT

SafeBridge Certification in potent compound safety is based on the successful implementation of the “systematic approach” to potent compound safety (see sidebar). The on-site assessment includes evaluation of both physical plant and equipment items (such as air pressure

A SYSTEMATIC APPROACH TO HANDLING POTENT PHARMACEUTICAL COMPOUNDS

1. Review and Evaluate the Hazards Associated with Pharmaceutical Drug Substances and Drug Products

- Review current compound handling practices of potentially potent compounds or compounds of unknown toxicity
- Evaluate toxicological/clinical data and put into occupational health categories (Occupational Health Categorization System)
- Review physical/chemical properties of the drug substance or product, including explosivity and static electricity potential
- Conduct process hazard reviews to integrate appropriate environmental, health and safety activities into manufacturing operations (for example, evaluating fire protection and risk management issues, containment and control technology options, disposal considerations)

2. Develop Standard Operating Procedures

- Develop written procedures for handling and disposal of pharmaceuticals in a production and laboratory environment in general based on their occupational health category, e.g., Category 3 compounds should be handled in enclosures or contained systems
- Develop written procedures for specific operations such as: weighing, proper use of laboratory hoods, proper use of powders weigh hood, the appropriate personal protective equipment to wear with certain categories of compounds and conditions, proper procedures during the addition of drug substance, etc.

3. Develop Training Program

- Train employees in potent compound safety and product handling practices and/or toxicology
- "Train the Trainer" - Train the environmental health and safety or other staff on potent compound program elements
- Develop video on specific handling practices for a potent compound or process
- Train supervisors and management on the business necessity of incorporating health and safety systems into product development and appropriate safety culture ("Supervising for Safety")

4. Develop "Tools" to Evaluate and Measure Exposure

- Develop Occupational Exposure Limits (OELs), "safe" limits based on existing data for occupational exposure to a compound
- Develop industrial hygiene (IH) sampling and analytical methods for compounds to allow monitoring of the workplace to occur

5. Design and Develop Containment and Controls; Verify Effectiveness

- Design containment approaches for hazard
Approaches that have been used for potent compounds include:

- Glove box technology	- Isolation technology
- Powders weigh hoods (laboratory)	- Vertical process trains
- Intermediate bulk containers	- Special valving
- Ventilated enclosures	- Local exhaust hoods
- Glove bags	- Vacuum transfer
- Validate performance of engineering controls by IH monitoring of containment devices during handling
- Perform health surveillance with special emphasis on evaluating target organs potentially affected by exposure

6. Determine and Assess the Environmental Impact of the Drug Substance or Product and Associated Manufacturing Processes

- Conduct short-term and cost effective "screening" environmental fate (i.e., persistence) and effects tests to determine the proper disposal procedures for waste streams from pharmaceutical operations
- Assess the impact of pharmaceutical and chemical processes on environmental regulatory compliance and/or the site emission profile
- Develop the Environmental Assessment (EA) portion of the Investigative New Drug (IND) or New Drug (NDA) Application to FDA, including physical/chemical properties, fate and effects, and manufacturing information

relationships, containment, and process technology) as well as assessing program items such as process safety, training, medical surveillance, and industrial hygiene..

A company is considered certified after an on-site assessment by two experienced and board-certified SafeBridge health professionals and achieving the minimum scoring requirements of the sixty-point evaluation in the following four broad areas:

1. Program Management

This assessment area evaluates the company's commitment to proactive management of and continuous improvement in potent compound safety. Important elements include clear assigned responsibility for potent compound safety issues, a system of goals and objectives for the management team in this area, defined budget

support for improvements, involvement of the EH&S function in related business decisions and change control, and development and implementation of a strategic plan. Appropriate skills to implement a potent compound safety program need to be available to the company (from either internal or external resources) including industrial hygiene, safety, engineering, toxicology, industrial hygiene analytical chemistry and occupational medicine.

2. Hazard Evaluation

This area evaluates the company's ability to bring the appropriate occupational health assessment tools for the proper categorization (or banding) and limit setting of pharmaceutical compounds; analytical chemistry to develop sensitive air monitoring methods and to analyze samples; industrial hygiene to conduct air monitoring, to

interpret data and to recommend exposure controls; and occupational medicine to establish a health surveillance program to identify potentially at-risk workers and to identify and treat the first signs and symptoms of occupational disease.

The hazard identification process goes beyond the "traditional". Safety Data Sheets (SDSs) are a minimum hazard evaluation tool. However, SDSs rarely have sufficient information for the type of toxicological evaluation necessary to determine the pharmacological potency and toxicity category of an API or an intermediate and never have sufficient information for the development of an Occupational Exposure Limit (OEL). Manufacturing contractors and other third parties need to implement a detailed questionnaire to obtain further relevant information on toxicity and pharmacological potency from the supplier in order to conduct an appropriate risk assessment.

Hazard evaluation may also need to include additional product testing (toxicological, environmental and safety) to adequately assess the risk. Such testing may be critical to "fill in the blanks" on new compounds for the benefit of both the contractor and the supplier. It is not uncommon to share costs for such data development.

Industrial hygiene "tools" such as monitoring equipment should be available. The hygienist needs training so that representative air-monitoring surveys to evaluate exposure potentials are properly conducted.

Reports of such surveys with conclusions should be written and communicated to workers that may be involved in the relevant processes.

3. Containment and Controls

This program area is the most important and therefore is the most heavily weighted in the Certification assessment. A company must place the emphasis for exposure control on containment at the source of dust generation and have process engineering controls such as isolators, closed charging and discharging devices and local exhaust ventilation in place. Facility features such as airlocks, pressure gradients, changing facilities and a decontamination misting shower are also warranted. Personal protective equipment (PPE) is required but it must only be used as a redundant control. This is the necessary and appropriate establishment of the hierarchy of controls.

Among some of the other elements to be evaluated in this area are process sampling containment, controls such as ventilated balance enclosures and bench hoods in the support laboratory, factory acceptance criteria and on-site qualification testing for control equipment and a personal hygiene policy.

4. Communication

Proper communication in potent compound safety includes administrative controls such as SOPs that contain potent compound elements and development of effective training programs. Batch sheets should include key hazard information and proper precautions and PPE requirements. SDSs should be readily available to all employees. Access to appropriate medical evaluations and any industrial hygiene records including conclusions and recommendations should be established. A specific potent compound awareness training program is required. An accident and incident investigation system should be in place. Training programs in all relevant health and safety regulatory areas is required and professional development opportunities should be made available to the primary persons responsible for potent compound safety.

PHASE 3 - SUMMARY REPORT AND GRADING

A written Certification report detailing the results of the assessment and recommendations for improvement for each major area covered by the assessment is developed. The report includes findings, comments and recommendations based on the evaluation of each of the sixty criteria points. Each criterion and each of the four major program areas will be graded.

SafeBridge has developed a unique scoring system that objectively rates the company's potent compound safety program status. Percentage scores based on degree of implementation and integration are applied to each criterion. The four areas are weighted differently reflecting the relative importance of the area. The score for each program area is averaged and the average score is multiplied by the weighting factor for the given area.

A minimum overall score of 65% must be achieved with none of the four program area scores under 55% to receive a Letter of Certification. An overall score of 80% would qualify as an industry leader. If the company does not meet the minimum criteria in each major area of assessment, then confidential recommendations will be provided on how best to accomplish the minimum criteria. Certification is given for a two-year period with a requirement that the company submit a self-evaluation at the end of one year for SafeBridge to review.

After two years, another on-site visit by one board-certified health professional from SafeBridge is required to maintain Certification.

IMPACT OF THE CERTIFICATION PROGRAM

These criteria were developed after years of implementing successful occupational health programs inside the pharmaceutical industry and the scoring is based on the degree of implementation of proven systems for the prevention of occupational disease.

The Certification program and the related Gap Analysis program (utilizing qualitative rather than quantitative scoring) have been used at numerous companies to assess their capabilities, including big pharmaceutical companies. Contract manufacturers that have achieved SafeBridge Certification have found it to be effective in the prevention of occupational health effects in workers and in attracting potential clients to their facilities.

To date two companies that manufacture APIs for other parties, Ferro-Pfanstiehl in Waukegan, Illinois and Tetricons in Madison, Wisconsin, have achieved Certification. Several other companies in the U.S., Canada and Europe have been evaluated using the criteria in a Gap Assessment format for the purpose of self-improvement or third party evaluation for suitability as a potential contract manufacturing partner. Other companies have requested Certification information and are about to begin the process.

SafeBridge Certification is a unique and recognized system for evaluating the safe handling and production of highly potent active ingredients, and when an organization achieves Certification, it is a hallmark of competency in worker protection.

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