Safe Handling of Potent Active Pharmaceutical Ingredients (APIs) in Kilogram Quantities

Sergio Cesco-Cancian, Christopher Nilsen, Kirk Sorgi, and Xini Zhang

Chemical & Pharmaceutical Development – Early Development, Raritan, NJ 08869 USA

Abstract

The development of potent compounds with therapeutic benefit reduces the amount of material that a pharmaceutical company needs to generate for dosing. However, when microgram quantities of Active Pharmaceutical Ingredients (APIs) produce a therapeutic effect and kilograms are synthesized to meet demand, special programs need to be put into place to limit exposure to such compounds in order to keep personnel safe.

Our research and development facility used to prepare APIs for use in First-In-Human clinical trials will be used as a representation of state-of-the-art technology for producing kilogram quantities of potent compounds up to a level of Performance-Based Occupational Exposure Limit (PBOEL). Category 3 in accordance with Johnson & Johnson Safety & Industrial Hygiene guidelines.

Introduction

In the case of APIs of lower toxicity, the major driving force in design is to prevent the possibility of product contact with the free environment. For APIs of high potency, the major concern in design is to protect the workforce from the hazardous material. This has led to the use of barrier technology, downward laminar flow booths and other containment technology. Innovative design solutions are required to provide practical answers to the problems of contamination and cleanliness.

In the case of the Raritan Large Scale Synthesis Center (LSSC), a major issue is that materials are being produced for use in toxicological studies and early phase clinical trials where such materials are unlikely to have a defined Occupational Exposure Limit (OEL). Thus, the level of containment required is set by other means.

Each company sets its own criteria to determine the level of containment and controls necessary to ensure the safety of its employees. Johnson & Johnson's Safety & Industrial Hygiene (S&IH) group has developed a system to assign compounds a Performance-Based Occupational Exposure Limit (PBOEL). Based upon information available on the compound or class of compound. The Raritan LSSC is capable of handling PBOEL Category 3 compounds.

Facility Design

Our facility is capable of handling Category 3A compounds in a shirt-sleeve environment and Category 3B compounds with increased Personal Protective Equipment (PPE).

The facility utilizes a filter dryer to contain potent solids from those precipitated in a reactor to both plate filter and agitation dry contents. The dried solids can then be directly transferred into an intermediate bulk container (IBC) for either use at the reactor (see α/β valve above) or for transfer to bags in an isolator (below).

Guidelines

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>Categorie I</th>
<th>Categorie II</th>
<th>Categorie III</th>
<th>Categorie IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>POTENCY</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>OCCUPATIONAL EXPOSURE LIMIT (OEL)</td>
<td>2000 μg/m³</td>
<td>1000 μg/m³</td>
<td>500 μg/m³</td>
<td>250 μg/m³</td>
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<tr>
<td>Contraindications</td>
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<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>PPE</td>
<td>Full protective gear</td>
<td>Reduced protective gear</td>
<td>Reduced protective gear</td>
<td>Reduced protective gear</td>
</tr>
</tbody>
</table>

The use of solids charging systems that utilize split-butterfly valve (α/β) technology (above left) greatly reduce the risk of user exposure during reactor charging steps. Also, appropriate sampling systems (above right) are necessary to reduce user exposure to potent compound streams.

Engineering Controls

The downward laminar flow booth showers the user in air that keeps contaminant concentrations in the user’s breathing zone to ~200 μg/m³ in front of the booth and in the center of the inside of the booth.

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Cleaning

- Contamination/Cross Contamination is a major concern, especially in high potency situations where minute amounts of compound could produce a therapeutic effect.
- Stringent cleaning protocols necessary
- Testing for cleanness (perhaps down to single-digit ppm or “not detectable” level essential
- Floor sweeping not permitted
- HEPA vacuum systems

Maintenance

- Equipment needs to be on a strict maintenance schedule to ensure proper operation.
- Equipment should be accessed for maintenance from outside of the containment area where possible.
- Safe change (BI/BO) HEPA filters where needed

Training

- Cannot be overemphasized
- System fails without training on equipment, controls, PPE, and cleaning
- Not knowing or following proper procedures in this potentially dangerous environment is the most common root cause of injury

Suggested Reading


