Piramal
Pharma Solutions

SAFE HANDLING OF HIGHLY ACTIVE COMPOUNDS

INTRODUCTION

Our facility located in Lexington, Kentucky is a unique parenteral manufacturing site that uses isolator technology to manufacture sterile products with varying degrees of pharmacological activity in the same facility. The risks associated with handling highly pharmacologically active products (some term as potent or cytotoxic) can cause concern in the industry; however experts in toxicology, industrial hygiene, chemistry, safety, and quality assurance agree that a risk-based approach to safety is most appropriate.1, 2 There are no regulations or guidelines that prescribe a mandated approach or require segregation of products based on pharmacological activity. There is, however, a lot of interpretation and misunderstanding across the industry.

The current risk-based approach to safety relies on two basic concepts:

1. Define a safe level of exposure (for both worker safety and cross-contamination concerns)

2. Reduce the potential for exposure through cleaning controls or using dedicated equipment to minimize risk of exposure

There is no requirement to use dedicated facilities or even dedicated equipment.The prevailing opinion is to control by risk mitigation on a case-by-case basis.

The first approach establishes acceptable exposure limits to protect workers and mitigates risks of cross-contamination, most often through establishing Occupational Exposure Limits (OELs). This approach employs toxicological information (LOEL, NOEL, ADE/PDE, TTC) to define an OEL in micrograms per cubic meter of workplace air. This is intended to designate the acceptable levels a healthy worker can be exposed to without yielding an adverse response to a drug. In most cases OELs will drive the cleaning control limits that ultimately are geared to minimize worker exposure.

Additionally, a new movement is afoot to look at “health-based acceptable daily exposure limits” (ADEs) as well as Occupational Exposure Limits.1, 2 This approach considers that people potentially exposed through cross-contamination (mainly patients) may not be an “average healthy worker”. While this theory is relatively new, an example is the manufacture of a pediatric drug or one that is generally administered to an elderly patient. In both cases, the patients may respond differently than a “healthy worker” and require different controls for mitigating the risks associated with cross-contamination.

The second approach to minimize risk of cross-contamination and exposure is focused on the use of equipment and cleaning. The most simple risk mitigation tool uses product-dedicated equipment. This is the only way to eliminate cross-contamination risks. Unfortunately, the use of dedicated equipment bears a high price tag that is often economically impossible in its purest form, which would essentially require dedicated manufacturing facilities. The second approach is to

conduct MAC calculations (Maximum Allowable Carryover) to establish cleaning limits for multi-purpose equipment. These take into account the toxicity of the product being cleaned from and the therapeutic dose of the product to be made after the cleaning is completed. The idea is to reduce the risk of a carryover event to ensure that less than 10% of the lowest observed effect level (LOEL) of a highly active or toxic product is present in the maximum dose of the next product being manufactured in the same equipment. This is a sound approach, but yields a limitless number of possibilities for cleaning requirements and methods because of the highly variable product list and production schedule at most manufacturing facilities, particularly those of a contract manufacturer. While this approach is manageable, it can be very complicated and does not allow for much flexibility in scheduling.

We have created a balanced approach to the safe handling of highly active compounds that maximizes safety while managing the economic factors. Our operational principles capture the best of both approaches into a redundant system protecting the patients who take our products and our employeeswho manufacture our products. The primary means for mitigating the risk of cross-contamination lies in our use of equipment. All product contact equipment/surfaces are considered dedicated or disposable at Piramal. Secondary surfaces or multipurpose equipment that is not designed to have product contact, are cleaned and swab released to cleaning limits based on an OEL to ensure our workers' safety. Since products would only come in contact with these surfaces under low probability circumstances that would typically result in rejected product, the risk of cross-contamination is de minimis. The end result is a system with controls in place to protect a "healthy worker" from exposure to our products and minimize any risk for our products becoming contaminated.

While no regulations or guidelines dictate segregation of products based on pharmacologic activity, the risks associated with potent manufacturing are significantly diminished through a risk-based approach to safety, such as the procedures in place at Piramal.

References
International Society for Pharmaceutical Engineering, Baseline Pharmaceutical Engineering Guideline, Volume 7, Risk-Based Manufacturing of Pharmaceutical Products, September 2010.

Sargent EV; Faria E; Pfister T and Sussman R: (2013) Guidance on the establishment of acceptable daily exposure limits (ADE) to support Risk-Based Manufacture of Pharmaceutical Products, Reg Tox Pharm, 65: 242-250.

Piramal Pharma Solutions is a contract development and manufacturing organization (CDMO), offering end-to-end development and manufacturing solutions across the drug life cycle. We serve our clients through a globally integrated network of facilities in North America, Europe and Asia. This enables us to offer a comprehensive range of services including Drug Discovery Solutions, Process & Pharmaceutical Development services, Clinical Trial Supplies and Commercial supply of APIs and Finished dosage forms. We also offer specialized services like development and manufacture of Highly Potent APIs, Antibody Drug Conjugation and are well versed in technologies such as Bio-catalysis, Route Scouting etc. Our capability as an integrated service provider & experience with various technologies enables us to serve Innovator and Generic companies worldwide.

Piramal
Pharma Solutions

Piramal Pharma Solutions, Agastya Corporate Park
Kamani Junction, Kurla (West). Mumbai 400 070. India.
Email: contactus@piramal.com
Call: +91 (0)22 3802 3000

piramal**pharmasolutions**.com