

Q&A WITH AJINOMOTO BIO-PHARMA SERVICES: — ARE YOU PROTECTING YOUR EMPLOYEES — DURING HPAPI MANUFACTURING?

The biopharma industry has increasingly moved toward more potent and selective active pharmaceutical ingredients and, while this has had great therapeutic advantage, it can pose risks to those employees who manufacture these highly potent active pharmaceutical ingredients (HPAPIs) and final drug products. It can also be challenging for drug developers to locate contract manufacturing services that are able to manage the very low occupational exposure levels (OELs) associated with these unique products. This is particularly challenging when developing and manufacturing highly potent injectable and infused biologics. The crossroads of current good manufacturing practices (cGMPs) and low OELs can involve some of the most complex engineering, product quality, and industrial hygiene challenges found within the pharma industry.

Tom Evans is the director of safety, health, and environment (SHE) at Ajinomoto Bio-Pharma Services (Aji Bio-Pharma), which recently commissioned a new high potent aseptic vial filling line. His team's role in this project, along with Karl Kasai at Kasai Consulting, is to ensure Aji Bio-Pharma can effectively produce a client's drug using HPAPI without risk of exposure to facility personnel, a critical factor in successfully bringing many of today's novel highly potent drugs to market. In this Q&A, he discusses the resources and capabilities necessary to do so.

Life Science Connect: What was your area of focus while designing and commissioning the new aseptic fill and finish line?

Tom Evans: The risk of exposure to personnel is a major concern when developing and manufacturing highly potent materials and compounds for new drug products. That is why our focus was to develop containment strategies that allow employees to work with these therapeutics in a production environment and effectively control the risk of exposing them to occupational illness. Quantifying risk in this way requires a discipline called occupational toxicology, which ensures the relative toxicity of a novel drug is well known and characterized so we can then develop appropriate engineering and

administrative strategies that will effectively protect our production employees. The discipline that drives testing and challenging of the performance of your overall strategy is called industrial hygiene. Having a skilled occupational toxicologist and a pharma-experienced industrial hygienist is imperative in this type of project.

LSC: How do you identify the toxicity of an API to determine what controls need to be put in place to protect personnel?

Evans: During early phase drug development, you typically do not have all of the information you need to assign and publish what we call an occupational exposure limit, or OEL, since this requires toxicology and other clinical study information that is, in general, not available yet. An accurate OEL is required for developing a robust strategy for implementing effective engineering controls, administrative controls, and personal protective equipment assignment. But if you do not know how toxic something is, or how it may cause occupational illness, it may be difficult to develop the best approach for keeping employees safe. Instead, you must rely upon the best available information and assessment of a skilled occupational toxicologist to assign occupational exposure bands, or OEBs, which are a

range of categories based upon toxicity or assumed toxicity created from the available data and information of similar molecules. Each band then has subsequent handling, engineering, administrative, and personal protective equipment control strategies associated with it, a concept that is similar to the more well-known CDC-NIH Biosafety Levels. It is typical for there to be one to five bands, with one being the least toxic and having the least strict handling procedures, and five being the most toxic, with the most stringent handling requirements.

When we begin working with a client, we ask for information about their product, such as its phase of development, toxicology screening data, and drug metabolism and pharmacokinetics data. If they have not already had a skilled occupational toxicologist develop an OEL or assign an OEB, we will collect the necessary information from them and send it to our consulting occupational toxicologist. Based on the review of that data, the occupational toxicologist will assign it either a true OEL, if there is enough information to do so, or an OEB. This allows our industrial hygienists and SHE personnel to understand how we should handle that compound in the laboratory and/or production environment.

LSC: Why is the creation of detailed user requirement specifications important when designing an HPAPI aseptic fill-finish production line?

Evans: When you think theoretically about OEL, and drug manufacturing in general, you really cannot create a 100 percent zero-exposure environment. However, the allowable permissible exposure level associated with some of these compounds is very, very low. And you can't assume you can apply standard 8-hour time weighted average (TWA) calculations when performing employee exposure and industrial hygiene studies. The compounds with potential toxicity levels of concern are well below what is visible to the naked eye. Therefore, a strong understanding of your desired containment performance target (CPT) for production equipment is critical. It is imperative that the CPTs that are developed align with the materials you're going to work with. This should be part of a detailed user requirement specification document that outlines this engineering strategy along with all of the other standard equipment use specifications, such as materials of construction, throughput, vial size versatility, accessibility, cleanability, etc. In other words, everything you want your equipment to have and do. From there, you must still build and install the equipment, which begins one of the most

critical parts for SHE professionals: challenging and testing the containment performance. You must understand your performance limitations when working with HPAPI. The health and safety of your employees depend upon it.

When doing this, it is necessary you bring all project stakeholders to the table, as one discipline may know a little bit about the other. However, it requires subject matter expertise in all the disciplines to be able to pull this off correctly. Due to the small margin of error when working with HPAPIs, you do not have the luxury of using too many generalities.

LSC: How should this information and the strategy based on it be communicated?

Evans: Some vendors that make the containment equipment used with HPAPIs cannot promise a containment performance target that is low enough for some of the drugs currently in development. Again, we are talking really low airborne concentrations, which may be less than 5 nanograms per cubic meter. Less than 5 nanograms per cubic meter represents the high end of our lowest OEB range. Therefore, it is imperative that you develop a strategy that challenges your equipment to determine if it can function appropriately at the level you desire. When we are working with a client, we make sure they understand these challenges with equipment as well as the work that goes into containment performance testing. It is important they know that it is not possible for every result to be at the target point and that there may be areas that are questionable. We like to think of CPT test results as "actionable" and/or "no action required." Actionable requires more studies in order to reconcile that information from a risk management standpoint. When you are working with targets this low, it is not enough to just say whether the equipment "passed testing." Even minute quantities of highly potent materials can cause problems in terms of employee exposure.

Finally, an experienced SHE manager is needed to tie all of the containment testing data together so that it can be clearly communicated to the client as well as to employees and management. There will be different subsets of employees involved with production, some of whom are highly technical and others who are part of a more general labor force. It is a very fair question for all levels of employees to ask how their company is protecting them and why things are done the way they are. It is our obligation to have science and data-based answers they can easily understand to help them feel comfortable and safe doing their jobs.

LSC: As you know, GMP and ISO compliance come with their own system for ensuring quality, which is critical in biopharmaceutical manufacturing. How do you reconcile the GMP and ISO paradigm with best industrial hygiene practice?

Evans: When working in an aseptic production environment, the GMP strategies, which employ ISO standards, are about product protection from contamination, whereas industrial hygiene practice focuses on containing the contaminant within the space and, therefore, away from the employees. This means it's essential to create a positive pressure contaminant-free environment that meets the GMP and ISO requirements as well as create a barrier between that space and the outer space where the employees are, so they are not subject to exposure. Ultimately, it becomes an engineering feat to create a positively pressured internal space and a negatively pressured external space. At Aji Bio-Pharma, we overcome this using airflows and filtration within a specially designed isolator from a company called SKAN. The air going in and out of the isolator travels through a HEPA filter, ensuring any contaminants collected in the airflow from the isolator are being captured.

LSC: What are some of the common issues that can go wrong when installing this equipment? How can one avoid making these?

Evans: Most of the isolator companies are hesitant to specify user performance targets that are at low nanogram levels. And typically, the filler companies are not the companies that make the isolators, so you must integrate two companies to create a fill line that is properly contained. Along with these challenges, many of the companies that sell the isolators and fill lines for these types of applications are international, which creates some logistical challenges. The equip-

ment is built elsewhere, so you must have robust factory assessment testing to ensure you are involved with the design, construction, and factory testing before it comes to your site. These companies must also work well together. Having a general contractor who understands the complexities and can make sure the equipment is installed correctly is key.

LSC: What ongoing monitoring should be in place to ensure the system is functioning as intended?

Evans: It becomes part of your normal industrial hygiene monitoring to make sure the equipment is functioning properly and that you are doing everything to protect your production employees. This is a minimum requirement. As a leading CDMO, we always strive for best available technology and practices, which is necessary when providing services to a wide range of clients and projects. We must evaluate the toxicity and potency of new products and regularly ask ourselves questions about our capabilities, such as will our equipment be able to properly contain these materials? Will we be able to inactivate the material and remove it from equipment surfaces? Our system uses vaporized hydrogen peroxide for inactivation; therefore, when we do not know for sure that this will inactivate a highly potent product, we cannot proceed with the project. This requires testing and confirmation. Quite often, this is not a question that the drug developer, our client, has needed to answer thus far. Due to our diverse mix of clients, we are always prepared to take on whatever role is most suitable for our clients' needs. With some clients, we will take on the role of SHE educator and provide guidance, while others, typically the large pharma companies, are skilled in this area and have very specific questions about our industrial hygiene program. It's a lot of fun to share our story and begin a new relationship.

Overall, there is a considerable amount of work and expertise necessary to make sure employee exposure to toxic materials in a facility manufacturing HPAPIs is below the acceptable limits. As biomanufacturers venture into the rapidly growing market of HPAPIs, it is important to consider whether they have the resources and capabilities to protect their product and their employees. The lack thereof can threaten not just the ability to provide an appropriate working environment for their employees but also the ability to safely bring their drug to market.