WHITEPAPER

Manufacturing of Highly Potent APIs with Best-Practice Safety and Containment Control Procedures

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Highly potent APIs are pharmacologically active substances that exhibit biologic activity at extremely low concentrations, such as a daily therapeutic dose of <10 mg or an occupational exposure limit (OEL) of <10 µg/m^3 as an eight hour time-weighted average. Approximately one quarter of all new chemical entities and around half of those in clinical development are estimated to be highly potent, with the overall global market for HPAPI expected to increase from $16.5 billion in 2017 to $26.8 billion in 2023 at a CAGR of 8.7%.

It is a key regulatory and safety requirement that prospective hazards associated during the handling of HPAPIs are identified and understood to enable the development of Occupational Exposure Limits (OEL). Together with other factors including Short-Term Exposure Limits (STELs) and the physical properties of an API, the definition of an OEL plus associated health risk classifications enable organizations to conduct risk assessments for operators working in HPAPI facilities. These risks can include various acute, allergenic, corrosive, carcinogenic, mutagenic, toxic, reproductive, and other occupational health hazards.

These assessments can then be used to establish and maintain safety and containment control best practice procedures that minimize exposure risk regardless of manufacturing stage or production site. Conformance to pharmaceutical regulatory requirements and ICH guidelines also requires a thorough consideration of other quality and safety procedures to prevent the release of an HPAPI or intermediate, or cross-contamination with other products manufactured at the site.

Due to the significant challenges and costs required to ensure-high levels of safety during development, scale-up and manufacturing of HPAPIs, it has become increasingly common for pharmaceutical companies to outsource production to specialist contract manufacturing organizations (CMOs). There are many CMOs which market HPAPI capabilities. However, to reduce technical and scale-up risk, it is most common for pharmaceutical companies to select a partner with a proven track record in the commercial manufacturing of HPAPIs, as well as a full range of small-scale development labs and large-scale commercial reactor volumes. It can also be advantageous to select CMOs that have core competencies in other related advanced technology areas for a specific HPAPI project, as well as additional capabilities for the development of oral and parenteral formulations and final drug products.

The world's largest CMO site for HPAPI is Evonik's Tippecanoe Laboratories facility in the U.S. State of Indiana. The site has a total capacity of 170 m^3 to handle compounds with an OEL down to 0.1 µg/m^3 with reactors ranging from lab-scale up to 7,600 liters. Originally established by Eli Lilly, the site has been operated by Evonik since 2010 and now serves more than 20 pharmaceutical companies. The T29 facility in Tippecanoe has supported the safe handling of HPAPIs since the early 1990s. The Tippecanoe site has had six consecutive FDA audits without a form 483.

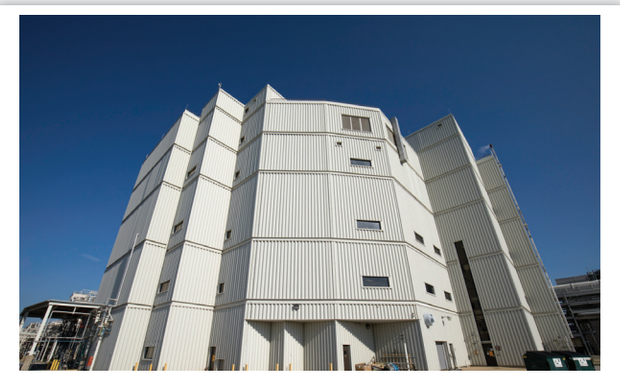

Figure 1. The T29 facility at Tippecanoe Laboratories

The multi-unit, multi-product facility was designed from day one to achieve both effective product cross-contamination protection as well as worker safety. A broad team of industrial hygienists, maintenance teams, operations teams, quality assurance experts, engineering, and automation experts were involved in the initial creation of the design. Following its construction, extended validation and qualification efforts were completed to demonstrate the facility not only met initial performance criteria, but would also sustained optimal performance over time.

Five years of industrial hygiene air monitoring data was gathered to evaluate containment for all processing and handling steps. These studies enabled the development of continuous improvement and innovation for all containment systems. To support this long-term outlook, a background contaminant monitoring surveillance program

was implemented to detect any deterioration of systems over time in frequently performed reviews by a professional industrial hygienist. Both qualitative and quantitative risk assessment methods were consistently applied. Furthermore, methods for clearance monitoring after equipment cleaning, and for unplanned release scenarios, were validated. At the same time, the chemical process safety and control aspects are consistently monitored via a central control room (see Figure 2).

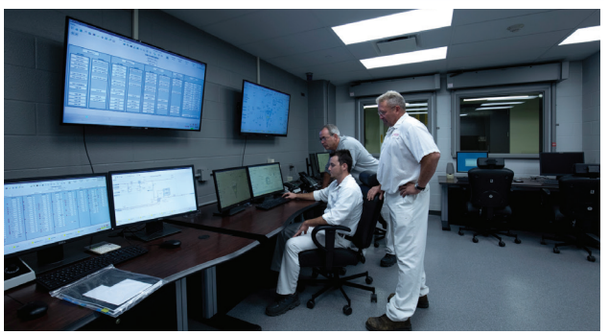

Figure 2. The central control room of T29.

As a result of these and other activities at the T29 site, virtually all routine operations are now verified for the effective handling of potent compounds down to the less than 100 ng/m^3 OEL without the use of personal protective equipment (PPE). Respiratory and dermal protection are only required as precautionary measures or in case of process excursions.

With at least three generational turnovers of T29 operators over more than 25 years of operation, one key factor that has helped sustain the facility's containment performance record has been the provision of comprehensive training for new personnel, as well as continual refresher training for existing personnel. This program utilizes a combination of classroom training, as well as extensive on-the-floor training. A strong emphasis is placed upon the demonstration of containment techniques by trainees under the tutelage of skilled instructors. Training modules make extensive use of video and fluorescent materials to create visual feedback for trainees.

The success of T29 also highlights that the ability to sustain operational effectiveness within a HPAPI facility requires a full set of additional technical resources, management systems and the full engagement of various technical groups. This includes quality assurance management systems and programs for inspection, testing, calibration and preventative maintenance (see Figure 3). Continuous improvement processes for facility infrastructure and equipment, including upgrades to digital process control systems (DCS) and material transfer technologies, have led to the ability to manufacture multiple HPAPI steps in parallel, enabled faster campaign change-overs, and increased the practical capacity and throughput of the facility.

For the site itself, it is important to ensure that warehouse and dispensing operations are capable of handling potent compounds

Figure 3. Continuous maintenance and calibration tasks are consistently carried out at T29.

and on-site waste treatment and disposal systems are in place for both hazardous and non-hazardous solids and liquid wastes. For personnel, it is also important to staff a quality control laboratory with a full array of analytical methods, employ on-site industrial hygiene specialists, and maintain an internal toxicology team for the development of hazard classifications, occupational exposure limits (OELS), and equipment cleaning limits based on ADEs as per ICH and EMA guidelines.

Key parties and processes that should be utilized under a comprehensive best-in-class system for hazard assessment, risk assessment and risk control are summarized in Table 1.

	Hazard Assessment	Risk Assessment	Risk Control Systems
Involved parties	▪ Industrial Toxicologist ▪ Toxicology Review Committee	▪ Industrial Hygienist ▪ IH Technicians ▪ Quality Assurance Specialists ▪ Operations Personnel ▪ Engineering	▪ Industrial Hygienist ▪ Engineering ▪ Maintenance ▪ Analytical Laboratories ▪ Operations Personnel

Utilized processes	▪ Hazard Classification
	▪ Dose/Response Evaluation
	▪ Safe Exposure Levels (OEL's, STEL's)
	▪ Derivation of Acceptable Daily Exposure (ADE) values
		▪ Control Strategy
		  ▪ Engineering Controls
		  ▪ PPE Selection
		  ▪ Administration Controls
		▪ Reproductive Risk Assessment
		▪ Operator Awareness
		▪ Operator training
			▪ Cleaning Methods and Limits
			▪ Air Space Monitoring
			▪ Spill Procedures
			▪ Operating Procedures
			▪ Facility Controls
			▪ Process-Specific Controls
			▪ Waste Handling
			▪ Medical Surveillance
			▪ Respiratory Protection
			▪ Emergency Response

As demand for the production of HPAPIs becomes more widespread across the pharmaceutical industry, CMOs must continue to invest in the continuous improvement of infrastructure, equipment, programs, and staff. The need for sophisticated and highly precise quality and safety systems has also increased, with the development of a new class of ultra-potent compounds used in targeted delivery forms such as antibody drug conjugates. In addition to its large-scale capabilities for HPAPI, Evonik has also established a cGMP suite for small-scale production of highly potent compounds with an OEL down to 0.05 µg/m^3. Evonik will continue to invest across its quality control and development assets in Tippecanoe, as well as other related technologies and manufacturing sites for HPAPI and highly potent drug products, to serve the emerging requirements of the pharmaceutical industry.