

TRENDS IN High Tox Manufacturing

A look at the regulations and hazardous characterizations driving the market

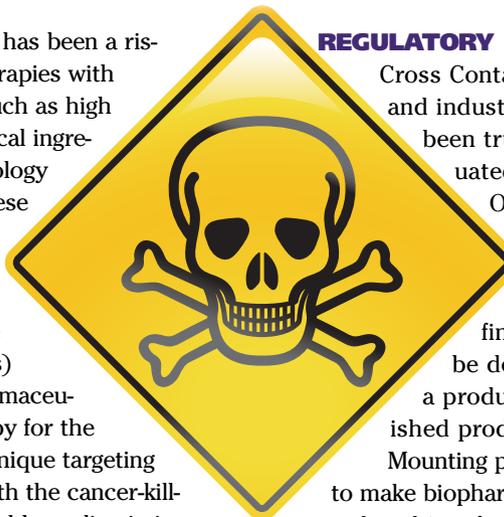
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Over the last few years, there has been a rising demand for targeted therapies with high potency compounds such as high potency active pharmaceutical ingredients and certain cytotoxic drugs. Oncology appears to be the leading domain for these products and increased use in the treatment of certain cancer indications has gained much attention due to the low dosage requirements and lower side effects. Antibody-Drug Conjugates (ADCs) are a new class of highly potent biopharmaceutical drugs designed as a targeted therapy for the treatment of cancer. By combining the unique targeting capabilities of monoclonal antibodies with the cancer-killing ability of cytotoxic drugs, ADC's are able to discriminate between healthy and diseased tissue, in contrast to traditional chemotherapy agents which attack both. The ADC's can target and attack the cancer cells so that healthy cells are less severely affected. With over 25% of drugs manufactured worldwide being classified as highly potent¹, this market is currently cited as one of the most important segments of pharmaceutical industry.

Due to the special containment requirements for manufacturing highly potent active pharmaceutical ingredients and cytotoxic drugs, we have seen many Contract Manufacturing Organizations (CMO's) invest in building additional capacity in this area. While there are tremendous benefits and a strong promise with these types of products there are also considerable challenges and risks associated with their production, especially in a multiproduct CMO environment.

Due to their high toxic properties, the manufacturing of these high potent compounds presents both an occupational exposure risk to personnel and a product cross contamination risk to next product batch manufacturing and adjacent process areas, requiring special attention to their containment. There can be occupational hazards if the proper engineering controls are not deployed and the products are not handled carefully. In addition, cross-contamination with other products can present significant occupational, regulatory, and patient risks. Therefore, adequate containment strategies and proper classification of hazards are essential for the manufacture of highly potent active pharmaceutical ingredients and cytotoxic drugs.

This article discusses the regulatory environment and hazard characterization currently driving the future of high toxic pharmaceutical manufacturing.



REGULATORY DRIVERS

Cross Contamination: A primary focus of regulatory and industry guidance over the last 10+ years has been truly based on **“Risk”**; with risk being evaluated **to patient safety and product quality**.

One of the leading areas of identified risk is associated with cross contamination during manufacturing of Active Pharmaceutical Ingredients (APIs) and final dosage forms. Cross contamination can be defined as a detrimental contamination of a product (starting material, intermediate or finished product) with a different product.

Mounting pressures on industry to control costs and to make biopharmaceuticals economical to the public are a key driver for industry to utilize effective and efficient multi-product and multi-purpose facilities to the greatest extent possible. The risk of cross contamination in these multi-product, multi-purpose facilities, processing higher potency and specialty products has drawn the attention of industry professionals and regulators alike. In particular, the European Commission has issued proposed changes to *Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use* that specifically address cross contamination. The proposed changes to the Eudralex Volume 4 specifically addressing cross contamination are to Part 1; Chapter 3: “Premises” and Equipment and Chapter 5: “Production.”

Chapter 3: “Premises and Equipment; Production Areas”, (3.6) states that, “Cross contamination should be avoided by robust design of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by appropriate procedures and technical or organizational measures, including reproducible cleaning and decontamination processes of validated effectiveness.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk:

- a) Which cannot be adequately controlled by operational and/or technical measures or*
- b) Scientific data does not support threshold values (e.g. allergenic potential from highly sensitizing materials such as beta lactams) or*
- c) Threshold values derived from the toxicological evaluation are below the levels of detection”*

Chapter 5: “Production” continues on to define the requirements for a toxicological evaluation as the basis for



the establishment of threshold values for the products manufactured and provides examples of potential “operational” and “technical” measures. The toxicological evaluation is important for companies in designing and renovating facilities as it provides the basis to calculate projected product carryover in a forward-looking cleaning validation program. It pulls the cleaning validation program from an afterthought to the design phase where it can be used to make scientific based decisions. This “right sizing” decision making process can save companies money by preventing the overdesigning and overbuilding of facilities unnecessarily out of perceived risk rather than scientific rationale. Formalized Risk Assessments, employed as part of a company’s Quality Risk Management program must be based on the toxicological data of the products manufactured. The outcome of the Quality Risk Management process should be the basis for determining the necessity for, and the extent of, operational and technical measures. The appropriate measures may range from sharing the equipment and facility, to dedicating specific product contact parts or areas within a facility, and to the complete dedication of the entire manufacturing facility. The Risk Assessment data must demonstrate and justify that cross contamination is appropriately controlled in multi-product and multi-purpose facilities.

For companies that have been slow to react and implement Formal Risk Assessment processes as part of their Quality Risk Management program, the time to act is now. Documented Risk Assessments will be required to demonstrate to regulators that facilities and equipment are fit for their intended use. In the future the use of qualification documentation/protocols (IQ, OQ, and PQ) alone will not suffice without the support of formalized risk assessment documentation.

There are already many tools and guidelines that are available for developing and implementing formal risk assessment programs. *ICH Q9 Quality Risk Management* should be the foundation for a company to build and establish their policies and procedures. Other industry guidelines such as the *ISPE Baseline Guide for Risk Based Manufacture of Pharmaceutical Product (Risk – MAPP, Sep 2010)*, provides specific guidance as related to the identification of means of cross contamination and potential operational and technical measures to mitigate the potential risks.

Occupational Safety: Unlike most chemicals, a majority of pharmaceutical APIs Occupational Exposure Limits (OELs) have not been established by occupational safety regulatory or standard setting agencies, or organizations such as the US Occupational Safety and Health Administration (OSHA) and the American Conference of Governmental Industrial Hygienist (ACGIH). Since adhering to OELs is considered an effective and proven way to protect workers from developing deleterious health effects caused by chemicals, many pharmaceutical companies have opted to determine OELs for their drug substances for internal use. A brief description of the OEL setting process is summarized below.

A RISK BASED APPROACH FOR MANUFACTURING PHARMACEUTICAL PRODUCTS

I. Hazard Characterization

A risk-based approach for manufacturing pharmaceutical products comprises the following components:

1. Identification of hazards
2. Assessment of dose-response relationships
3. Establishment of health-based limit, both Occupational Exposure Limits (OELs) and Acceptable Daily Exposures (ADEs)

The (1) identification of hazards and (2) assessment of dose-response relationships are collectively referred to as hazard characterization. Performing a hazard characterization of the pharmaceutical products is critical to evaluating risks and deciding on appropriate exposure controls.

For hazard identification, a formal review of all available animal and human data should be performed for each pharmaceutical product. For the innovator companies that developed the APIs, the data used in the analysis should include the data submitted in the regulatory filing. Contract Manufacturing Organizations (CMOs) should request this information and the rationale for the setting of the OEL and ADE or PDE (permissible daily exposure) in the EU from the innovator company asking them to manufacture the pharmaceutical product. Generic manufacturers should evaluate each of the pharmaceutical products by searching public data bases for OELs and ADEs, as well as the database developed within their organizations. For the hazard characterization of the pharmaceutical product, the reviewer should have access to the full range of preclinical and clinical data required for approval of the drug. For non-proprietary compounds, all relevant information on the potential hazards of the material should be obtained through referenced databases. Standard toxicology and pharmacology reference texts should be consulted and a literature search (e.g., on PubMed) should be performed. Once all of the information and data has been compiled, the hazard characterization process should commence.

II. OEL Setting

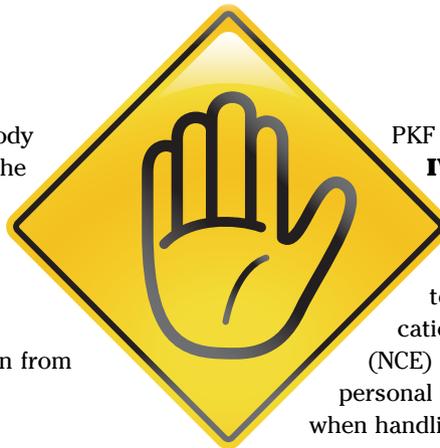
An Occupational Exposure Limit is the time-weighted average concentration of a substance in air to which it is believed that workers may be exposed, without personal protective equipment, for eight hours per day, 40 hours per week without adverse effect. An OEL may also have an associated Short Term Exposure Limit (STEL), to which personnel may be exposed for only 15-minute intervals, and/or a Ceiling or Maximum Acceptable Concentration, which should never be exceeded. Most innovator pharmaceutical companies establish OELs for their pharmaceutical products.

An example OEL calculation (expressed in milligrams or micrograms per cubic meter of air) is shown as:

$$\text{OEL } (\mu\text{g}/\text{m}^3) = \frac{\text{Dose (mg/unit time)}}{\text{UF}_c \times \text{MF} \times \alpha \times \text{AF} \times \text{V}(\text{m}^3/\text{day})}$$

Where:

Dose = The lowest dose associated with the critical effect(s), human or non-human.



Note: If the available dose is expressed per kg body weight, a body weight of 60 kg is assumed, and the dose is calculated accordingly before insertion into the above equation.

UF_c = Composite uncertainty Factor(s)

- UF_H = Inter-individual variability and seriousness of effect
- UF_A = Interspecies differences; extrapolation from other animal to human.
- UF_S = For extrapolating from short study duration to long study duration
- UF_L = Dose to Presumed No Effect Level (PNEI)
- UF_D = Database Completeness

MF = Modifying Factor(s)

α = Bioavailability Factor

AF = Accumulation Factor

V = Volume of air breathed in 8 hr. period (10 m³ per day for moderate work load)

III. ADE Setting

As with the setting of an OEL, the purpose of a hazard evaluation in setting the ADE is to identify all possible hazards associated with a pharmaceutical product and to rank hazards according to their severity. When combined with a dose-response assessment, the critical effect can be defined. This is typically the first clinically significant adverse effect that is observed as the dose increases.

The ADE is used to derive swab or rinse limits for cleaning validation purposes. In order to apply ADEs to specific subpopulations, further adjustments may be required to address a variety of uncertainties, as well as differences in bioavailability when extrapolating between different routes of exposure. Normally, the ADE is based on the data for the route that it will be applied to in the evaluation. If route-to-route extrapolation is necessary, a sound scientific rationale is required to support application to a different route.

An example ADE calculation (expressed in milligrams or micrograms per cubic per day) is shown as:

$$ADE (mg/day) = \frac{NOAEL \text{ mg/kg/day} \times BW (kg)}{UF_c \times MF \times PKF}$$

Where: NOAEL = No Observable Adverse Effect Level. If a NOAEL or NOEL is not available other values are used such as:

- LOAEL = Lowest Observed Adverse Effect Level
- LOEL = Lowest Observed Effect Level
- Lowest Therapeutic Dose (LTD)

BW = Body Weight

UF_c = Composite Uncertainty Factor(s)

- UF_H = Inter-individual variability or seriousness of effect
- UF_A = Interspecies differences; extrapolation from other animal to human
- UF_S = For extrapolating from short study duration to long study duration
- UF_L = LOAEL to presumed NOAEL extrapolation. Where a LOAEL is not available the lowest dose may be extrapolated to a PNEI using a larger factor as appropriate.
- UF_D = Database Completeness

MF = Modifying Factor(s)

PKF = Pharmacokinetic Factor

IV. Hazard Bands

Based on the hazard characterization and development of an OEL, APIs can be placed into hazard or control bands depending on their potency and toxicological effects. This is the first step in the identification of the hazard potential of the New Chemical Entity (NCE) or API and the associated exposure controls to ensure personal protection and minimize product cross contamination when handling potent and highly potent APIs. Each hazard/control band should be associated with safe handling guidelines that outline the appropriate facility, equipment, and administrative controls to ensure exposure is maintained below the OEL for the NCE/API. In general, a potent API is defined as one with an occupational exposure limit (OEL) at or below 10 µg/m³ and a highly potent API as having an OEL below 1 µg/m³. Good industrial hygiene practice dictates that the primary means to control personal exposure be engineering controls.

Containment equipment such as isolators, contained transfer systems, and other contained chemical and pharmaceutical process equipment are examples of these types of engineering controls in use today. Containment systems and equipment with integrated containment systems are being designed and used by bio(pharmaceutical) manufacturing facilities for all operations and for all dosage forms including solid, parenteral, and others, including inhalation and dermal, to control personal exposure and minimize cross contamination within a multi-product facility.

The process of selecting containment equipment and systems should include:

- 1) Perform a process review of the process steps, unit operations, and tasks (including charging/discharging, in-process manipulations, sampling, and cleaning).
- 2) Identify the APIs, intermediates, and finished products to be handled and processed, including their associated OELs and/or Hazard/Control Bands.
- 3) Set a containment performance target (CPT) for the process.
- 4) Specify and select the containment equipment and devices based on the task list and the CPT.
- 5) Verify containment performance by performing a factory acceptance test (FAT) and site acceptance test (SAT).
- 6) Evaluate containment performance and occupational exposure to workers during actual operations processing the NCE or API.

CONCLUSION

With the demand for these High Potency Active Pharmaceutical Ingredients continuing to increase, having an understanding of the regulatory landscape and utilizing a risk based approach to manufacturing these products is critical for pharma and CMOs interested in expanding or adding high-potency API capacity. Expanded use of these types of ingredients will continue to challenge manufacturing, quality and design professionals. Having a multi-disciplined team consisting of process technologists, industrial hygienists, regulatory compliance and cleaning validation personal assess the risks will result in a successful outcome for your project. ■

REFERENCES

- 1 Roots Analysis Private Ltd, HPAPIs and Cytotoxic Drugs Manufacturing Market, 2014-2024, August 2014