
# MANUFACTURING OF CYTOTOXIC PHARMACEUTICALS

## This high-risk sector of pharma manufacturing requires extraordinary attention to safety details.

**by Raymond E Peck, CEO of VxP Pharma**

Due to the inherently hazardous nature of cytotoxic agents, these drugs must be packaged, labeled and handled with extraordinary care. Several recent studies have found that the exterior surfaces 30 to 50 percent of vials and ampules delivered to pharmaceutical companies are contaminated with trace amounts of cytotoxic drugs.

In the interest of mitigating precisely these sorts of hazards, the International Society of Oncology Pharmacy Practitioners (ISOPP) published its Standards of Practice for the Safe Handling of Cytotoxic Drugs, in 2007. These guidelines recommend specific safeguards in the manufacturing, handling, transportation, packaging and labeling of cytotoxic agents.

The responsibility for preventing cytotoxic contamination lies squarely with pharma manufacturers and contract manufacturing organizations (CMOs). This article will explore several of the most critical warnings outlined in the ISOPP guidelines, and provide recommendations on counteracting those risks.

*Factors throughout the manufacturing pipeline impact the risk of cytotoxic contamination.*

## CYTOTOXIC DRUGS MUST BE CONTAINED, PACKAGED, LABELED AND TRANSPORTED WITH EXTREME CARE.

Successful containment of cytotoxic agents begins with the containers in which they are packaged. The risk of contamination is particularly acute in cases of oral and topical formulations, whose containers are designed to release their contents easily. Thus, manufacturers must take care to use resilient containment materials, in order to minimize the risk of leaks or other damage. The most effective approach may be to enclose the container itself within an outer shell of tougher plastic.

When packing cytotoxic agents or transportation, manufacturers should enclose the packages within high-impact foam, or another type of material capable of absorbing shocks and containing spills. All packages containing cytotoxic drugs must be clearly labeled, in order to be easily identified by all personnel involved in their transportation and storage. Although the ISOPP recommends adoption of a worldwide universal symbol indicating cytotoxic agents, this labeling currently varies among countries, necessitating extraordinary caution during the transportation stage.

In addition to caution labeling, all cytotoxic agents must be shipped with material safety data sheets (MSDS) that provide clear instructions for protection and decontamination in case of a spill. The MSDS must also include data on the physical and chemical stability of the drug, including requirements related to the drug's light and temperature sensitivities. These instructions will help ensure that the drug avoids unintentional damage during distribution and handling.

## FACTORS THROUGHOUT THE MANUFACTURING PIPELINE IMPACT THE RISK OF CYTOTOXIC CONTAMINATION.

Although safe packaging and labeling are crucial in the safe handling of cytotoxic pharmaceuticals, the ultimate responsibility lies with the manufacturing organization. Such an organization must take steps throughout its entire pipeline to ensure that all cytotoxic agents are manufactured in an environment free of contamination hazards, and are quality-controlled for maximum safety.

In fact, responsibility for a quality-controlled manufacturing process starts from the top down, with a system of corporate policies that mandate standard operating procedures for dealing with cytotoxic agents. Facilities must be designed and maintained in ways that quarantine cytotoxic handling and processing zones, and equipment should be selected based on its ability to be cleaned quickly and effectively after use. Staff must be trained on how to respond in case of a spill or breakage, and must be aware of all segregation, environmental containment, and procedural control standards in place.

Moreover, warehouses and other storage areas must also be designed to contain the risk of contamination. These areas must be carefully controlled in terms of temperature, humidity and light, and should be constantly monitored for environmental variations. Access to these facilities should be restricted by means of access cards and/or biometric scanners, and only trained and authorized personnel should be admitted at any time.

*Following GMP for cytotoxic manufacturing helps mitigate the risk of hazards.*

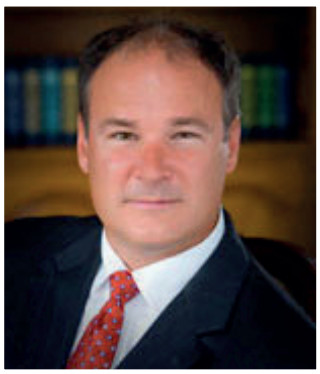
## FOLLOWING GMP FOR CYTOTOXIC MANUFACTURING HELPS MITIGATE THE RISK OF HAZARDS.

During the manufacturing stage itself, staff must diligently adhere to good manufacturing practices (GMP) for cytotoxic agents, as outlined in the ISOPP guidelines. These GMP include measures for handling and processing raw materials, preparing equipment, processing solutions, filling and finishing, and final cleanup. Checks and validations must be performed throughout each of these stages, in order to catch any potential contamination risk before it presents a hazard.

All raw materials, including glass vials, rubber stoppers, water for injection, and metallic caps must be sterilized in an autoclave or oven prior to use. Bulk solution must be prepared in quarantined tanks, preferably behind transparent panels. During the filling process, checks must be routinely performed to ensure effective dosage control, as well as correct fill weights and vial positioning. If the drug product is to be lyophilized (freeze-dried), pressure should be increased gradually during the cycle, in order to minimize the risk of product bubbling over within the vials.

Capping and stoppering should take place within the lyophilizer whenever possible. All filled containers should be integrity-tested, and inspected visually for defects. If the vials have come into contact with solvents at any point in the pipeline, staff should verify that the solvents have not erased any information (such as the product's expiration date) from the exterior surface of the vials. After filling, all equipment must be thoroughly cleaned by trained staff, and vials should be washed in an external vial washer. Finally, the entire facility should be scanned for any residue of cytotoxic product.

By implementing GMP for containment and segregation of cytotoxic product and related equipment, and by carefully monitoring all environments, manufacturers can often mitigate many of the worst hazards associated with cytotoxic pharmaceutical production. Even so, effective implementation of these GMP requires a staff of thoroughly trained experts, who maintain active awareness of safety measures, and of the manufacturing environment in which they operate.



In addition to being a writer and speaker, Raymond E Peck is the Founder and CEO of VxP Pharma Services and VxP Biologics, both based in Indianapolis Indiana.