Responsibilities of Manufacturers of Cytotoxic Drugs

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Abstract
In 2007, the International Society of Oncology Pharmacy Practitioners (ISOPP) published its Standards of Practice for the Safe Handling of Cytotoxic Drugs, which places a number of responsibilities on the manufacturers of cytotoxic agents. This includes the provision of contamination-free products. In particular, ISOPP would like manufacturers to provide information on the procedures used to limit contamination on the outside of cytotoxic products and documentation on the actual levels of contamination likely to be present. Another area of concern is the primary container and packaging of cytotoxic drug products. This must be produced to minimise the risk of breakage, and must be able to prevent leakage or spillage if breakage does occur. In addition, ISOPP asks manufacturers to label their cytotoxic products with a prominent and unique warning sign to clearly identify the contents as being cytotoxic in nature. ISOPP would like to see manufacturers work together with oncology pharmacists towards achieving best practice.

Keywords
Cytotoxic, contamination, drug manufacturers, packaging, labelling, transportation, stability

Packaging
All cytotoxic products for transportation from the manufacturer must be protected with high-impact-resistant moulded foam or other suitable packaging material to help prevent damage to the primary containers. The outer packaging must also ensure containment of cytotoxic spillage in the event of breakage.

Transportation
Manufacturers must ensure that all distributors of their products are aware of, and comply with, all packaging and transportation requirements until products are received at their final destination.

Labelling
Cytotoxic drugs must be easily identifiable by all personnel involved in their handling. The outer packaging of containers must display clear warning labels stating that the goods are cytotoxic in nature. Ideally, there should be a universal symbol adopted globally for cytotoxic agents; the symbol should be unique and instantly recognisable, and should not require workers to have language skills to recognise the hazard. Most countries have some recognised symbol representing cytotoxic agents. The symbol varies among countries, but in many cases it is purple and often contains a diagramatic representation of a cell in telophase. It may say ‘Danger/Caution Cytotoxic’, or may contain an exclamation mark. Whatever warning sign is attached, it should be clear and easily recognisable.

In many countries it is not mandatory for manufacturers to identify cytotoxic agents in this way. ISOPP strongly urges manufacturers to...
accept this responsibility and to adopt the policy of labelling all their cytotoxics with a prominent warning sign to alert all who may be involved in their handling. This applies to all dosage forms of cytotoxic agents.

**Chemical Contamination**

Since the late 1990s, several studies have indicated that vials and ampoules delivered from pharmaceutical companies may be contaminated on the outside with a cytotoxic drug.\(^2\)\(^-\)\(^7\) In some cases contamination has been detected in 30–50% of the vials examined. This may be the result of contamination generated during the manufacturing process or from inadequate washing of the vials before packaging. Many companies have now focused more attention on this problem, but with differing levels of success.

It is the responsibility of drug manufacturers to do everything possible to prevent or remove any contamination from the outside of cytotoxic drug vials or other primary containers. The goal must be to provide drug products that are free of external contamination. ISOPP demands that manufacturers guarantee that 100% of all batches are washed, and requests the provision of written documentation on the procedures used and on the validation of these processes. Manufacturers should provide some form of documentation (preferably from an independent laboratory) about the levels of contamination present on vials and other primary packaging of cytotoxics. Hospitals and buying groups should carefully consider the matter of external contamination when deciding which cytotoxic agents to purchase.

**Material Safety Data Sheets**

Manufacturers must provide material safety data sheets (MSDS) for all of their cytotoxic products, with explicit details on decontamination and protection measures to be taken in the case of a spill or accident.

**Stability Data**

Drug manufacturers must provide data on the physical and chemical stability of their products, with recommended storage conditions and requirements for light protection. This should include information on the stability of the agent after reconstitution and dilution to the usual concentrations seen in clinical practice, and should take into account the diluents and containers used by hospital pharmacies. If a glass bottle is recommended for preparation, manufacturers must ensure the availability of glass containers with an outer break-resistant material to be used specifically for cytotoxic agents.

**Consumer Medicines Information**

With the ever-increasing use of oral chemotherapy, it is vital that manufacturers provide comprehensive medicines information for use by pharmacists and patients. Many excellent educational resources for patients have been developed by drug manufacturers, and ISOPP encourages the continuation of this work.

**Conclusion**

Healthcare facilities continue to utilise valuable resources to develop and maintain occupational health and safety programmes to supply healthcare workers with the necessary training and equipment to minimise their exposure to cytotoxic drugs. In this article we have highlighted some areas in which manufacturers of cytotoxic agents must take on more responsibility for decreasing occupational cytotoxic exposure. In addition, by providing comprehensive drug information, manufacturers can further contribute to the safe and effective use of their products by both health professionals and patients. ISOPP looks forward to the pharmaceutical industry rising to this challenge and working together with oncology pharmacists and technicians to achieving best practice.

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Prevention of External Product Residue – A Risk-managed Approach

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The prevention of external residue on the outer surfaces of cytotoxic pharmaceutical products has been a significant concern for both manufacturers and medical professionals for decades. In recent times, with the modernization of concepts of quality management and assurance, the onus has been on conscientious pharmaceutical manufacturers to use both preventative and scientifically justified risk-based design and development approaches to assure the absence of potentially hazardous residues from external surfaces of primary packaging componentry. This ‘assurance’ of quality reduces the previous reliance on external washing processes. This article describes the holistic approach employed in Actavis Oncology manufacturing and distribution operations which assures the quality of products both on the inside and outside of the finished pack.

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Keywords

Cytotoxic, oncology, residues, packaging, cross-contamination, Actavis, risk-based

Historically, the pharmaceutical industry has concentrated its efforts on managing the safety, efficacy, stability, identity, purity and strength of the product within the drug product primary pack. In recent times, the cleanliness of the pack’s external surfaces has become of equal concern for toxic, sensitising or highly physiologically active products.

After decades of regulation and policies in healthcare institutions, workplace contamination from cytotoxic agents is still potentially a widespread risk, even in facilities that have made concerted efforts to foster workplace safety, according to studies presented at the American Society of Health-System Pharmacists earlier this year. Computer keyboards, lift buttons and flooring were just some of the areas found to be contaminated with cytotoxic agents, often several hundred metres beyond preparation areas that are specifically designed to prevent the spread of these potentially harmful substances.1,2

The risk of spread of cytotoxic agents within dispensaries, nursing stations and even the more general areas of hospital and medical centre premises is a challenge that cannot be taken lightly by any of the major stakeholders in the product provisioning and administration process, who include manufacturers, distributors, wholesalers, dispensary staff and medical practitioners.

Actavis is a leader in the development, manufacture and sale of first-class generic pharmaceuticals and is committed to managing all aspects of its business in a safe and responsible manner that protects the patient and the healthcare provider and promotes the health and welfare of employees and any related communities. The company has two facilities that manufacture sterile cytotoxic products for human use, one located in Bucharest, Romania and the other in Nerviano, Italy. Both facilities produce the following categories of sterile products: sterile lyophilised dosage forms – aseptically filled (freeze-dried powder/cake) and sterile liquid dosage forms – aseptically and solutions for injection.

The approach of Actavis to the prevention of cross-contamination and potential incidental transfer of product residues to the external surfaces of product primary packaging containers has always been one of prevention rather than cure. It considers that reliance on terminal washing processes to remove potential residues is too simplistic, and thus has striven to build quality (preventative) and risk-based approaches into all stages of the manufacturing and distribution process. With such a philosophy, the final container-washing process job is no longer difficult and the risk of product residues being transferred to hospital and medical staff from this source has been dramatically reduced.

Quality Systems

Modern pharmaceutical manufacturers strive on a daily basis to ‘manage’ the quality and reproducibility of their manufacturing and supply chain processes such that nothing (or at least very little) is left to chance. To this end, Actavis controls all of its manufacturing and distribution activities according to stringently defined procedures and systems and has a detailed and comprehensive corporate quality and environmental health and safety (EHS) manual, which clearly describes the company’s expectations of the quality and EHS systems that must be implemented at all manufacturing and distribution locations globally (see Figure 1). All operations are required to...
develop and implement detailed local procedures and practices to ensure compliance. Both the Sindan and the Nerviano sites have received approval from the US Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Device Agency (PMDA) and the EU’s regulatory agency. Both sites are also regularly inspected by client corporate quality assurance inspectors and by the internal corporate quality assurance department of Actavis, as well as being subjected to a schedule of self inspections to assure ongoing compliance with pharmaceutical current good manufacturing practice (cGMP). The Actavis quality system is based on a six-system model (the quality system and five product provisioning systems); Figure 2 shows the inter-relationship of the six systems. The quality system provides the framework for the product life-cycle management systems that function within it. This philosophy does not treat the five manufacturing systems as discrete entities, but instead integrates them to provide an overall culture of continuous control and compliance.

Facilities

Buildings are designed and maintained in such a way as to be aligned with the operations for which they are intended. Active product handling and processing zones are constructed using materials that are easy to clean and decontaminated with appropriate inactivating agents. In addition, those areas in which active materials will be exposed are designed using containment and isolation technologies against any potential spread of product residues. All facilities are constructed, maintained, cleaned and operated in accordance with cGMP and industry best practice. This requires that all cleaning and decontamination activities are clearly defined by procedure and that these standard operating procedures (SOPs) are validated by documented experimentation and challenge studies to prove their efficacy and reproducibility. Any spillage or breakage that might inadvertently occur during the manufacturing, packaging, warehousing or distribution processes is also controlled through the application of proceduralised and stringently trained practice. Facility design and routine maintenance focus on avoidance of product migration by segregation, environmental control, procedural control and risk analysis of the potential for active or product cross-contamination (see “Controlled Environments and Prevention of Cross-contamination”, below).

Storage and Distribution

Warehousing areas are designed to ensure logical and protective layout and environmental conditions. These areas are temperature- and humidity-controlled within pre-defined limits and are subject to continuous monitoring. Warehouse storage areas are clearly identified and protected from incidental shock and the risk of physical damage. Automatic card access control is implemented, and only trained and authorised personnel are admitted into warehouse areas (as in all the other areas of the facilities).

Packaging Materials

Primary and secondary packaging materials are considered critical elements. Components such as vials, stoppers and overseals are purchased only from the most well-known and reliable suppliers to the pharmaceutical industry. All suppliers are stringently inspected before approval and routinely thereafter. Components are strictly determined to ensure effective and reproducible standards. Specifications take account of container-closure fit and integrity, maintenance of product stability and processing characteristics. Vial design must preclude breakage and ensure stability during the filling and stoppering processes to avoid toppling and resultant product spillage. In addition, stability studies are routinely undertaken during development and on an ongoing basis to ensure that temperature effects (such as heating and cooling) do not affect container-closure integrity due to differential expansion/contraction, which could feasibly occur during transportation. Secondary packaging and shipping cartons are also carefully specified to protect products from breakage during warehousing and distribution.

Transport and Logistics

Actavis distributes all products via logistics partners who are licensed pharmaceutical wholesalers. Such partners operate in full compliance with good distribution practice for the storage and distribution of our products to the market. Distributors and logistics partners are all inspected and approved at supplier selection and routinely thereafter. Personnel are briefed and trained in the handling conditions and protective measures required for the distribution and delivery of cytotoxic pharmaceutical products.
The Manufacturing Process

Figure 3 details the individual stages of the manufacturing process.

Equipment Cleaning (Manufacturing)
Manufacturing equipment, including freeze dryers, filling machines, vessels, tanks and pipe work, is specified and designed to ensure it can be reproducibly cleaned with a high degree of efficacy. Where feasible, such cleaning is automated using clean-in-place (CIP) systems that use programmable logic controller (PLC) cleaning parameters, such as contact time, pressure, revolving/machine speeds, solvent jet...
orientation and temperature. All cleaning procedures are validated to ensure reproducibility and consistency. Cleaning validation is requalified on a pre-determined regular basis or in the event of a processing change that is deemed to be significant (after risk assessment). Cleaning validation is addressed as part of each site’s validation master plan (vVMP), which is reviewed for qualification status on an annual basis.

**Quality Control Laboratories**

The quality control (QC) laboratories, both chemistry and microbiology, are spatially separated from the production areas/ facility to further reduce the risk of potential cross-contamination. The laboratories are designed to accommodate the testing procedures and processes performed within them and to house the specialist testing instrumentation. The laboratories are constructed to avoid the risks of product sample mix-up and cross-contamination. Personnel are required to wear dedicated gowns in laboratory areas; the gowns cannot leave the analytical facilities, thus reducing the risk of product residue spread. The laboratories have their own warehousing space that is adequate for the storage of retention samples and product documentation and records. Laboratory equipment and glassware are also cleaned using validated, automated processes that ensure the inactivation and removal of product residues.

**Controlled Environments and Prevention of Cross-contamination**

Actavis has a documented policy in terms of the prevention of cross-contamination coupled with a cleaning validation policy for facilities handling active pharmaceutical ingredients. These policies comply with the European Chemical Industry Council (CEFIC)/ European Federation of Pharmaceutical Industries and Associations (EFPIA) Guide to Good Manufacturing Practices for Active Pharmaceutical Ingredient Manufacturers. Compliance is reflected by the ongoing focus on prevention through design, environmental control, procedural control and risk analysis of the potential for active or product cross-contamination. This focus on preventing cross-contamination by design and procedures is predicated by both the competent regulatory agencies and the Actavis quality systems, as detailed above, as well as being assessed and challenged in regular Actavis EHS audits. Such reviews are Control Of Substances Hazardous to Health (COSHH) and risk-based, focusing on:

- containment – using isolation equipment, e.g. total enclosure, partial enclosure, local exhaust ventilation (LEV);
- segregation – using controlling procedures;
- monitoring – using instrumentation to confirm environmental barriers are operating; and
- training and staff awareness (ongoing) – ensuring control measures are understood and complied with.

To ensure and secure the integrity of the active pharmaceutical ingredient and excipient raw materials through to the finished product, enhanced localised room air barriers (both negative and positive), air cascades throughout the facilities, positively pressurised isolators, negatively pressurised glove boxes and access security control measures eliminating the entry of unauthorised personnel are used. When process changes or enhancements are made, such modifications are managed by formal risk-based change control procedures, which ensure a review of the potential risk of cross-contamination as part of the assessment.

**Vial Cleaning and Ongoing Checks**

The industry standard of cleaning validation has been applied, demonstrating the effective removal of product residue using purified water for washing of the most challenging cytotoxic formulations using a worst case, bracketed approach. Cleaning process validation is carried out to clearly define the process parameters following initial development of the process (including water pressure, water flow, machine speeds, contact time, water temperature and water jet orientation). Cleaning assessment is carried out using swabs. Cleaning process validation is requalified on a pre-determined regular basis or in the event of a change that is deemed to be significant.

**Cleaning Validation Grouping**

Cleaning validation has been performed by bracketing, product grouping and selecting the worst case in each group. Separating products into groups and choosing the worst case relies on both scientific data and data resulting from operational experience. To aid grouping, products have been given assessments based on active substance solubility in the employed solvent and toxicity. Any new molecule is assessed separately.

**Analytical (Evaluation) Methods**

All analytical methods used to demonstrate the low residual limit for external washing of the vials are high-performance liquid chromatography (hPLC) methods. All analytical methods applied are the most appropriate/best available and are validated according to current Internation Conference on Harmonization (ICH) and cGMP guidelines, taking into account the factors set out in Table 1.

**Ongoing Checks of External Product Residue**

Each batch of product (vials) is 100% visually or optically inspected (depending on the product) for vial defects, particulate matter, cosmetic defects and evidence of product residue on the outside of the vials. This inspection is carried out by highly trained operators with the systems being challenged and validated to confirm that they can detect an inspection problem.

**Vial Shield**

Vial Shield is a transparent polymer shrink-wrapped sheath that covers the vial from the aluminum cap crimp to and including its base. It is applied to the vial following external cleaning, inspection and labelling. Actavis believes that the addition of Vial Shield has the following benefits (see Figure 4):

- the protective base significantly reduces the chance of breakage if the vial is dropped;
- the sleeve wrapped tightly around the vial from the bottom of the base to the top of the crimp keeps the glass in place if a breakage does occur, thus reducing any spillage of product or splintering of glass;

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<tr>
<th>System Suitability</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Specificity</th>
<th>Limit of Quantitation</th>
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<td></td>
<td>Repeatability</td>
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Using validated methods for cleaning vial outer surfaces for product residue, all results were found to be below detection/quantification limits.

### Table 1: Method Validation Parameters

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• Vial Shield provides an additional layer of protection between the dispensing clinician and the product; and
• Vial Shield protects the batch number and expiry date from being erased by the action of solvents (isopropyl alcohol [IPA]) used to sanitise the outer surface during the patient administration process.

Conclusions

As described, nothing within the manufacturing of cytotoxic parenteral products is left to chance. Actavis actively ensures the external cleanliness of its vials from cytotoxic residues primarily on a preventative basis by exclusion, containment and process design employing systematic risk-based approaches. Actavis has identified the following as being the main challenges in the prevention of surface residue: incoming primary packaging inspection, filling, lyophilisation (freeze-drying), packaging for transportation and incidental vial breakage.

The risk represented by vial breakage or leakage is managed by sourcing high-quality vials and effective container closure systems (stoppers and aluminium caps). Incoming primary packaging items (vials and stoppers) are inspected for defects that might cause product leakage. In consultation with both of our approved glass vial and stopper manufacturers, major elements of the process, storage and transport have been improved where possible. In addition, manufacturing and packaging equipment is designed, validated and maintained to prevent any incidental breakage.

Checks are routinely employed during the filling process, including dosage control, fill weights, vial positioning during filling and vial stability, to ensure that the product is accurately filled into vials, avoiding spillage. The lyophilisation (freeze-drying) cycles are designed and validated to apply controlled ramping of pressure to avoid bubbling over and migration of the product.

Any spillage that inadvertently occurs during manufacturing is contained and removed following clearly documented procedures, executed only by trained people.

In addition to these preventative measures, all vials are washed externally at the final stage of the production (see Figure 3) using an external vial washer. This equipment is specifically designed to carry out the washing of vials and is used in conjunction with an appropriately validated cycle.

Secondary packaging, including boxes for shipment, has been designed where feasible with the prevention of vial damage as a primary objective.

Although there is currently no finite acceptance criterion for external product residue defined either in cGMP or EHS legislation, at Actavis we have applied a policy that is coherent with industry guidance and best practice for the prevention of cross-contamination, cleaning validation and decontamination.

On the basis of the considerations described above, Actavis is confident that:

• its comprehensive approach to the prevention of cross-contamination and incidental product migration are in full compliance with cGMP/EHS guidance;
• proactive measures taken to prevent the possibility of external product residues are effective; and
• additional means to remove the unlikely occurrence of external product residues are appropriate.

We continue to keep a close check on the development of new techniques, technologies and legislation defining the way we and the rest of the pharmaceutical industry operate in this area. Finally, in line with other manufacturers of cytotoxic products, we recommend in product information leaflets that vials should be handled with care (using gloves and other containment measures).