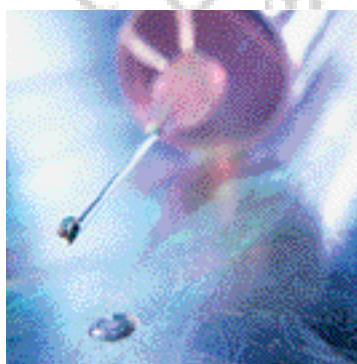


# Isolator Technology With the Patient in Mind

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Nothing can come of nothing, but the contamination of a drug can come from everything. Selecting the appropriate barrier system for protecting the product and/or the environment requires a logical approach while recognizing the various routes of possible contamination in the aseptic processing chain.

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The ultimate goal of pharmaceutical manufacturing is to satisfy the patient. We do this fairly well because we are all potential patients. Among the various problems regarding pharmaceutical development are those related to the production of sterile or toxic products. Sterile products such as injectables—except those compatible with terminal sterilization—must proceed through the uncertainty of the aseptic process under the strict regulations and constraints issued by the US Food and Drug Administration and the European Commission's European Agency for Evaluation of Medicinal Products (1, 2), which aim to isolate production as much as possible from its surroundings (see Figure 1).

Toxic products are defined by the risk they pose during their processing, either by their operator exposure level if the molecule has been subjected to toxicological trials for its classification or by the cautionary “one molecule” theory, which notes that risk exists even from one molecule of a particular product. In either case, this risk leads to performing the process with a defined segregation between the product and the personnel and/or production environment.

The challenges of protecting both the product and the personnel and/or environment mirror one another and have been discussed in the “isolation continuum” of PDA's Technical Report TR 34 (see Figure 2). Three main aseptic design choices are possible: cleanrooms, barrier systems (or *restricted access barrier systems*), and isolators. All aim to deliver a high-quality fine chemical of the active pharmaceutical ingredient (API) to the patient.

What techniques can be used to ensure the appropriate system is selected using a logical approach? Two recent publications help drive this choice for aseptic processing by providing qualitative information (experiences) (3) and by using an analysis method (4). In the first publication, Friedman describes eight case studies demonstrating the effects of poor personnel practices and the loss of environmental control. Select key points include:

- “Intensive aseptic activity by personnel was considered the likely vector of contamination.”
- “Poor handling of sealed glass vials, following aseptic processing and final packaging, was considered the root cause of the nonsterility.”
- “The essence of CGMP is the principle that every production phase through to packaging must be robust.”

- “The sterile drug manufacturer’s change control system was expected to assess whether the modified-grade filter continued to be suitable for its intended use.”
- “lack of a preventative maintenance program”
- “No validation assessment was done when the firm scaled-up the process.”
- “The firm used the same manufacturing approach when producing lots destined for parenteral dosage form as that for oral solid dosage forms.”
- “The problem was due to inadequate cleaning and sanitisation.”
- “Once such contamination becomes airborne and is allowed to proliferate unchecked, it is not a simple task to bring the environment back under control.”
- “Aseptic gowning by personnel was inadequate.”
- “Personnel introduced the contamination in the course of a difficult (and routine) aseptic manipulation of sterile equipment prior to the filling stage of the process.”
- “The firm did not adequately assess the risk posed by construction activities.”



Figure 1: An aseptic filling line isolator.

These case studies demonstrate that the routes of contamination are diverse and can originate from the very beginning of the API production process to the storage area of final product. The conclusion states, “The trend toward modern design concepts includes a general movement toward closed and semiclosed systems and away from personnel-intensive aseptic processing”

The second publication, by Murgatroyd, intends to help the reader make the optimal technical, financial, and logical choice for a segregation method. The selection is based on the “Kepner–Tra goe” evaluation technique, which is one of many risk-assessment methods. Ranking and rating parameters of the various aseptic process steps are the core of the analysis that lead to the choice among conventional cleanrooms, barrier systems, and rigid isolators. Possible contamination from personnel is a major factor that must be taken into account when making this decision. From the operator’s gowning protocol to the method in which the operator is to a lly or partia lly isolated from the surrounding rooms, one must keep in mind that human beings carry particulate and microbial contaminants (5). Unfortunately, this point has been forgotten and put aside, thus leading to the conclusion that a conventional clean room has a better rating than a barrier system, which is better than an isolator. As the author says, “Honesty and avoiding preconceptions are key.” Taking into account the sources of contamination risk, we could instead—with an operator’s fair impartiality—stepwise analyze the process from the figures of particulate, chemical, and bi ocontamination perspectives and, accordingly, to the part of the process where it is relevant to apply the proper technical options.

Bio decontaminating the enclosures with vapor-phase hydrogen peroxide, validated with coupons of spores at  $10^4$  and  $10^6$  (1), is easier to conduct in a closed system than in an open ward that must be made airtight to avoid the risk of more than 1 ppm in the environment. This process sets the initial contamination-free level of the process area.

When a toxicity risk to an operator or the environment ex-

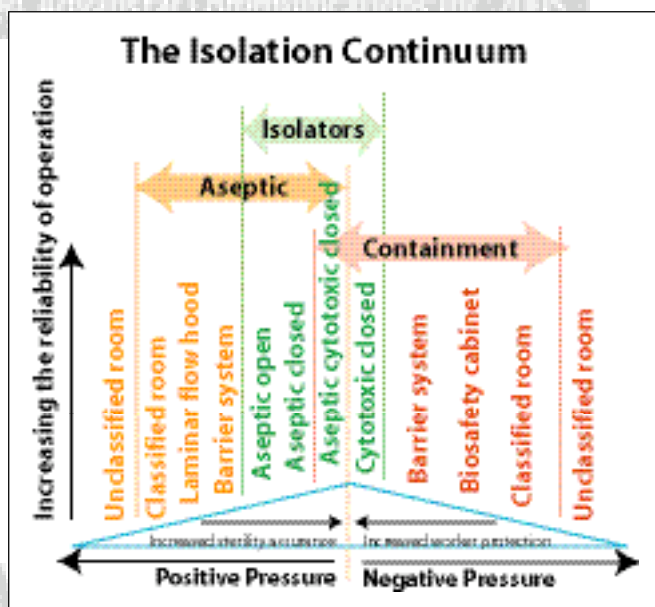


Figure 2: The isolation continuum.

ists, especially when processing a potent API, a strict gowning protocol with personal protective equipment is required when neither a barrier nor an isolator is implemented (6). The uncertainty is still there, however, even when an isolator is used (7, see Figure 3), because as for the two other techniques, an operator’s gloves can become punctured. The gloves must be tested “at work” and/or be safely changed. The end of such a process at the filling stage is, of course, a proper cleaning of the outside of the final container so as not to chemically contaminate the operators at the next steps of storage, distribution, and administration to a patient. (8).

Administering a drug to a patient is not always a single-step process, and in many cases, the sterile and/or toxic product (*e.g.*, an anticancer drug) must be reconstituted with a solvent in the proper administration setting. When performed at the bedside, this step may lead to adverse effects for nurses (8). Reconstitutions also must be secure in hospital pharmacies (9, see Figure 4). These reconstitutions are made in a clean room, a barrier

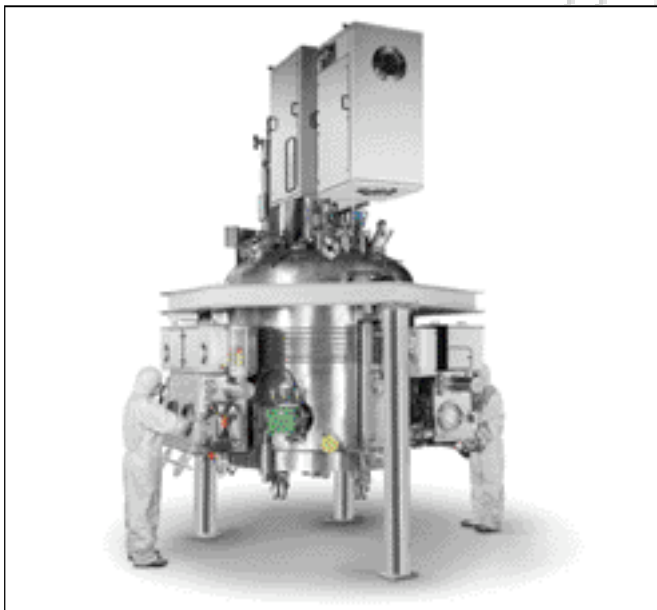


Figure 3: A filter-dryer isolator.



Figure 4: Cytotoxic reconstitution with isolator.

system, or an isolator with the same dilemma of choosing the appropriate system as the industry faces. In the United Kingdom and France, isolators are favored, even if these regions do not have a strict similar definition of isolators (10, 11).

Traditionally, UK manufacturers use negative-pressure isolators, which are designed to protect the operator and environment more than the patient. Conversely, isolators used in hospital pharmacies in France are mainly gas biodecontaminated positive pressure systems that, from a strict technical point of view, are positioned continuously to keep the sterility assurance level of the final product after reconstitution or compounding at the same level as each of its components. Both types of isolators are leaktight and separated from the environment by high-efficiency particulate air (HEPA) filters (>99.99% efficiency for 0.3- $\mu\text{m}$  particulates).

Manufacturers must choose not only between positive- or negative-pressure systems relative to the risk assessment, but also among various immediate surroundings and choices in ingress-egress personnel protocols, which may increase installation costs between, for instance, a Class B and a Class D room and upon the optimization of the operator work hours.

Even when the proper aseptic technique is used, the main risks of the aerosol form of a potent drug is that the drug can pass through HEPA filters and possibly through gloves. The risk is minimized with carbon filters on exhaust ducts and a routine that includes regular glove changes of validated quality.

Regulators prefer risk-assessment principles, risk analysis methods such as hazard analysis and critical control point (HACCP) and failure mode and effect analysis (FMEA), and decision trees to make choices. Risk assessment must be adapted in our industry and must be based on what is happening and could happen at the production floor and its environment. Before deciding on the proper environment, each step from API production to the administration to patient must be identified and weighed according to risk and must integrate the acceptable values of contamination provided by regulatory agencies as well as the recommendations within the lifetime of the equipment. Moving the stepwise production process toward quality efficiently without prejudice, requires the consensus of various relevant personnel, including operators, quality assurance/quality control technicians, maintenance supervisors, internal and external architects and engineers, buyers, and vendors.

My ongoing conclusion is that in times when the price of medication becomes an issue, especially for sterile and/or potent drugs, we must provide, through our empathy to the patient, an easy-to-use, safe product by controlling risk in a simple process.

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