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## **The Limitations of Isolators**

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Technical Paper

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Understanding the use of barrier isolators  
to comply with USP 797 and the NIOSH Alert  
on occupational exposure to hazardous drugs.

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## Abstract

This paper evaluates the use of isolators in pharmacy IV admixture programs to comply with USP <797> and the NIOSH Alert on preventing occupational exposure to hazardous drugs. A search of international pharmaceutical abstracts was conducted and analyzed for this evaluation. The literature confirms that isolators have limitations that prevent them from being the most effective answer to the NIOSH Alert. Isolators also only satisfy one aspect of the physical controls recommended in USP 797 as an alternative to a Class 100 hood in a Class 100,000 clean area. This research indicates that isolators are not the complete answer for compliance with USP 797 or the NIOSH Alert.

## Introduction

Two documents were released in 2004 that had major regulatory implications for United States' pharmacy IV admixture services.

1. USP 797. The U.S. Pharmacopoeia (USP) issued USP General Chapter 797, "pharmaceutical compounding – sterile preparations" in January. (<http://www.usp.org>) As of July 1, 2004, the JCAHO (Joint Commission for Accreditation of Healthcare Organizations) has adopted these standards for their own use. Even JCAHO readily admits that actual implementation of the recommendations is an ongoing process that will take several years.<sup>1</sup> In the meantime, some individual State Pharmacy Boards are beginning to include the new standards in their inspections.
2. NIOSH Alert. On March 25, 2004, the National Institute for Occupational Safety and Health (NIOSH) issued their Alert, "Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings." (<http://www.cdc.gov/niosh/docs/2004-HazDrugAlert/>) NIOSH is an arm of the better-known OSHA (Occupational Safety and Health Administration). OSHA will likely consider the Alert in its future regulatory influence on worker safety issues.

There is still debate within the pharmacy profession about the requirements necessary to comply fully with these trend-setting actions. However, what individuals can agree on is that past practices are going to change, particularly in hospitals. The extent of the changes necessary will be determined over time.

Pharmacists have many options to consider in complying with USP 797 and the NIOSH Alert. Isolators are one of these options. Unfortunately, by themselves isolators only comply with a very small part of USP 797. They also have major limitations that do not make them the most effective answer to the NIOSH Alert. The remaining sections discuss these issues in detail.

## Isolator Background

Isolators are used in a number of industries for sterile processing. Years ago, many pharmaceutical manufacturers adopted them to improve quality assurance and reduce capital costs by eliminating the need for complicated cleanrooms. However, barrier isolators are complex systems, depending on the particular isolator configuration selected. Some of those complexities are described in the following literature review.

After getting its start in industry, isolator technology became more commonplace in European hospital pharmacies in the early 1990s. In fact, a large number of the hospital pharmacy studies in the medical literature review describing experiences with isolators originate in France.

By comparison, the US hospital pharmacy market has been much slower to adopt isolators for a variety of reasons. Simple resistance to change is always an issue, but the lack of a compelling reason to change might be the greater reason.

Despite years of advocacy by organizations such as the American Society of Health-Systems Pharmacy (ASHP) and individual State Pharmacy Boards, improvement in hospital pharmacy admixture services has moved at a glacial pace. The publication of USP 797 will finally accelerate the pace of change in US IV admixture practice. The NIOSH Alert could have a similar long-term effect on the safe handling of dangerous drugs.

## Literature Review

A retrospective search of recent international pharmaceutical abstracts resulted in eleven articles describing relevant isolator experiences. Seven articles were of French (including one French-Canadian) origin, the majority being poster presentations from ASHP Mid-Year national meetings. Three articles were authored, or contributed to, by Hank Rahe of Containment Technologies Inc.(CTI), a US isolator manufacturer. A single US hospital pharmacy-based article appeared, and even it was sponsored by a French-Canadian isolator company.

Two of the CTI articles are concept overviews with a comparison of the features of several brands.<sup>2,3</sup> The third article was a comparison with cleanrooms that showed isolators to be equivalent to working in laminar flow hoods but more productive than working in biological safety cabinets.<sup>4</sup>

The lone US article indicated user satisfaction with the isolator in preparing ASHP-defined risk level 2 and 3 admixtures and about 10 cytotoxic admixtures per day.<sup>5</sup> The author concludes that isolators are more expensive than traditional laminar airflow hoods, but more cost effective than a full cleanroom, in part because of savings from using fewer gowns and gloves. Mention was made, however, that the protection from cross-contamination of the operator and product is just “theoretical.”

Most of the French articles described basic operations using isolators that indicate they are significantly integrated into French hospital pharmacy practice. Bussieres and Forest compared barrier isolators and biological safety cabinets and found them to be basically equivalent in contamination potential but suggested that more research was required to thoroughly understand the limitations of both types of equipment in comparable real-work practice environments.<sup>6</sup>

Other French articles and posters described isolator experiences but the results are difficult to extrapolate to other French pharmacies, let alone to American settings. One focused on workload and time spent, but the numbers generally just reflect the gross amount of time required to complete their own unique procedures.<sup>7</sup> Jeune et. al describes how the isolator works in a cleanroom, along with the processes used to assure product quality.<sup>8</sup> Rohrbach et. al make financial comparisons with isolators but the only major variable studied is whether the isolator was in their central pharmacy, or one of their decentralized satellites.<sup>9</sup>

The French isolator literature did identify some potential obstacles to the use of isolators. Bounoure et. al described a complicated system that required the sterilization of all IV fluid bottles, ampoules and sterile supplies with peracetic acid gas to minimize contamination prior to mixing in the isolator.<sup>10</sup> Such a system would be cumbersome for the operator and appears significantly more time consuming than traditional hood mixing methods.

Langouet et. al documented a 23-day shutdown of their isolator, primarily because of false positive sterility tests due to contaminated cotton swabs.<sup>11</sup> Technical manipulations of the isolator also contributed to the shutdown. For reasons not clarified in the study, certain pharmacy staff did not understand how to consistently use the isolator safely and effectively.

The most disturbing direct comparison article documented the results of mixing 5-fluorouracil (5-FU) in six hospital pharmacies, three using isolators and three using hoods.<sup>12</sup> Measurable amounts of 5-FU were found in samples taken from 83% of the isolators versus just 8.3% of the hoods. Furthermore, the protective shields of the isolators were found to be contaminated, even after cleaning. Other isolator components were also found to be vulnerable to contamination.

The same isolator article described how the contamination ended up in the external environment. While only 3 of 72 sites tested in the hospitals using hoods showed 5-FU contamination, 35 of the 72 samples tested in the hospitals mixing in isolators were contaminated. The translated abstract of this article appears in the NIOSH Alert section below because the implications are so important for understanding how isolators do not fully contain hazardous agents.

## Isolators and USP 797

USP 797 is a lengthy and comprehensive compilation of physical, procedural, training and quality assurance standards meant to assure process quality throughout the entire complex sterile compounding system. The document includes dozens of suggestions and standards for handling tasks as diverse as personnel training and evaluation, quality assurance, validation, physical facility cleaning, environmental monitoring, finished product release checks and tests, product storage, end product expiration dating, maintaining product quality after the compounded items leave the pharmacy, patient monitoring and so on.

Out of these numerous requirements, isolators only satisfy one aspect of the physical controls as an alternative to a Class 100 hood (ISO Class 5) in a Class 100,000 (ISO Class 8) clean area. An isolator does not address the numerous physical environment standards in USP 797.

Unfortunately, another reason that some pharmacists are considering isolators is a misunderstanding of what kind of “cleanroom” is required by USP 797. USP 797 does not require sophisticated cleanrooms. What it does require is environmental control in the sterile compounding area that provides air quality of at least ISO Class 5 (3,520 particles of 0.5  $\mu\text{m}$  or larger per cubic meter). This issue has been widely misunderstood in pharmacies.

There are six levels of ISO (International Organization of Standardization) cleanrooms from ISO Class 3 to ISO Class 8. ISO Class 5, formerly known as Class 100, requires a maximum of 100 particles per cubic foot. This is the level required by USP 797 for the actual mixing area, and is the level met by the typical laminar airflow hood. Mixing IVs in a hood is nothing new for the pharmacy.

For the general area around the IV preparation area (or buffer area), USP 797 requires particulate levels of ISO Class 8, formerly Class 100,000. That is, a maximum of 100,000 particles per cubic foot. The chapter mentions a couple of other issues, such as an ante room for dressing etc. but Class 100,000 air quality is the primary requirement.

Implementing the most basic steps of straightening up an IV room, coupled with a positive pressure air system, will result in a room with less than 10,000 particles per cubic foot. Getting an IV room to less than 100,000 particles per cubic foot is quite easy by following the simple USP 797 physical facility suggestions.

The net result of USP 797 is to require mixing in a properly maintained laminar airflow hood (ISO Class 5) that is situated in a relatively clean room (ISO Class 8). These particulate quality requirements are not difficult to meet, and the only challenge is developing a process for testing the environmental controls.

There is plenty of room to debate every facet of USP 797 but it is not a radical departure from what reasonable admixture programs should already be doing. There are many basic steps in quality sterile compounding that some inpatient pharmacies have had neither the time, nor the resources, to implement. Regulatory agencies such as the FDA and State Boards of Pharmacy have long recognized this need. USP 797 simply puts the answers in a standard format for inspection and verification.

USP 797 promotes process control and quality throughout the entire sterile product preparation process. The physical location where the actual mixing takes place is a small component of the overall physical and procedural requirements. As such, an isolator is not the answer to addressing USP 797.

## Isolators and the NIOSH Alert

The NIOSH Alert is intended to protect healthcare workers from exposure to hazardous drugs. Whether OSHA adopts these standards, or not, the trend is for increasing safety practice and guidelines for healthcare workers handling hazardous and experimental drugs.

Isolators are designed to separate the outside environment from the mixing process, not to contain dangerous drugs. Any spills or aerosolization in the mixing chamber contaminate the outside of the mixed IV container and the inside of the isolator itself. When the finished product leaves the isolator, the outside environment becomes contaminated. Retrospective wipe studies have shown extensive pharmacy IV room and nursing area antineoplastic drug contamination through this mechanism when using vertical flow hoods.

The lack of containment is the biggest limitation for isolators in complying with the NIOSH Alert. A real-world example was described in the French six hospital isolator versus hood comparison article referred to earlier.<sup>1</sup> Environmental contamination was about ten times more prevalent from isolator preparation than in hoods. The article summary says it most concisely:

*The level of contamination by the fluorouracil in drug preparation was determined in six hospital pharmacies, three using hoods and three using isolators for the preparation of antineoplastic agents. Contamination by 5-fluorouracil of the work environment as well as the protective shield was measured by high-performance liquid chromatography with UV detection. Extraction was realized from 1 mL sample with 2 mL mixture.*

*Measurable amounts of 5-fluorouracil were detected in 83 % (10/12) of the samples in protective shield for isolator against 8.3 % (1/12) for the hood. The protective shields of isolators were contaminated even after cleaning. Contamination of the work environment was found for three samples among 75 for hood and 35 samples among 72 for isolators. The isolator gloves (Neoprene), the manipulator suit and the sleeve were potentially permeable.*

*This type of study shows that exposure of manipulators to cytotoxic agents can be controlled only if all the possible sources of contamination are identified and if suitable systems of protection are used. Analysis of surface samples of work environment and of the surface of preparations should be included in the validation procedure.*

One effective answer to containing hazardous compounds is the PhaSeal® “closed system” referred to in the NIOSH Alert. PhaSeal is designed not only to support a sterile result but to protect the drug mixer, drug administrator and the entire hospital environment by fully containing all forms of the hazardous drug. The disposable system allows pharmacy technicians and nurses who handle and administer hazardous drugs to comply with the recommendations in the Alert.

## **Conclusion**

Isolators only help facilities comply with a small part of the USP 797 physical facility standards by replacing the need for a laminar airflow workbench. However, the intent of USP 797 is far more comprehensive than physical controls. It is a scientific approach to IV admixture compounding that will require hospital pharmacies to review their entire system from start to finish. Isolators alone do not come close to providing USP 797 compliance.

Further, isolators were designed to provide protection for the IV admixture from outside contamination, not to contain the byproducts of the mixing process, such as aerosols and droplets. One article documented that over ten times as many hospital sites were contaminated in the three hospitals using isolators as in the three hospitals using hoods. This limitation is probably the biggest obstacle to isolators being an effective answer to the occupational exposure documented in the NIOSH Alert.

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