

# HAZARDOUS DRUG HANDLING AND INVESTIGATIONAL DRUGS: LESSONS TO LEARN

In this article, Marino Kriheli, Co-Founder of Equashield, discusses the need for closed-system transfer devices when handling hazardous drugs, particularly as they relate to investigational drugs, not only as key to patient and healthcare practitioner safety, but also in the context of upcoming US regulation.

Almost every drug contains some level of hazard, some are acute while others carry serious long-term risks. In the US, the National Institute of Occupational Safety and Health (NIOSH), a division of the Centers for Disease Control (CDC) under the Department of Health and Human Services, issued an alert in 2004, providing guidelines on how to identify and handle several specific categories of hazardous drugs (HD). According to NIOSH, a drug can be considered hazardous if it meets one of six health risk criteria:

- Carcinogenicity
- Teratogenicity or other developmental toxicity
- Reproductive toxicity
- Organ toxicity at low doses
- Genotoxicity
- Structure and toxicity profiles of new drugs that mimic existing drugs determined hazardous by the above criteria.

NIOSH maintains and updates its list of HDs every two years. NIOSH's 2016 list of HDs contained some 217 drugs, and NIOSH has proposed adding approximately 22 new drugs to the list in

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2018. Although antineoplastic agents make up a large portion of the list, there are non-antineoplastic agents that constitute a significant part of it as well.

Within its listing, NIOSH divides HDs into three categories:

- 1) Antineoplastic agents with manufacturer’s safe handling guidance
- 2) Non-antineoplastic agents with manufacturer’s safe handling guidance
- 3) Non-antineoplastic agents that have reproductive risk.

## CURRENT GUIDELINES FOR HAZARDOUS DRUG HANDLING

The US Pharmacopeia (USP) recently introduced an updated chapter on hazardous drug handling guidelines – USP Chapter 800. These updated standards around safe handling provide the guidelines by which healthcare facilities must abide when handling HDs.

USP 800, coming into full effect on December 1, 2019, provides several key recommendations around safe handling practice. These include the use of biological safety cabinets and cleanrooms when compounding HDs, the requirement to wear personal protective equipment (PPE) when compounding and administering HDs, a strong recommendation to utilise a closed system transfer device (CSTD) when compounding HDs, and the requirement to use a CSTD when administering HDs.

### Why CSTDS?

NIOSH defines a CSTD as “drug transfer device[s] that mechanically prohibit the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system”. There has been a great deal of conversation around what constitutes a “good” CSTD. However, recent studies that



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have utilised NIOSH’s original proposed CSTD testing protocols, which assess how well a device contains vapours, have found that devices which are fully contained achieved the best results.<sup>1</sup> Effective CSTDs, those which fully contain hazards, are designed and proven to be able to:

- Prevent aerosol escape
- Prevent leakage
- Prevent microbial ingress
- Not contain acrylonitrile butadiene styrene (ABS) or polycarbonate
- Be used efficiently and backed by clinical data
- Be made with materials that are compatible with hazardous drug/solvents such as dimethylacetamide (DMA).

14 years since NIOSH’s original alert, which recommended the use of CSTDs for safe HD handling, and approximately one year before use of CSTDs is mandated in the administration of HDs, it is estimated that approximately 55–60% of US healthcare facilities use a CSTD to handle HDs.

#### WHAT CAN THE DRUG DEVELOPMENT INDUSTRY LEARN?

Drugs in development, or “investigational” drugs, pose a challenge. The healthcare industry is still uncertain on how to handle new drugs that are in the clinical trial phase. Often, investigational drugs are handled like non-HDs, simply due to lack of data on whether the drug should be considered hazardous. However, as a precaution, investigational drugs that are designed to treat diseases traditionally treated by HDs are considered hazardous by staff in healthcare settings. With this being the case, healthcare institutions should use the same safety measures that they would use when preparing HDs.

However, the challenge is that while healthcare institutions may want to use CSTDs for handling investigational drugs, they are often unsure about the compatibility of the device with the new drug. This issue was also raised in a 2018 Institute for Safe Medication Practices (ISMP) safety alert on investigational drugs, suggesting that “the vials/containers [of investigational drugs] are compatible for use with a closed system transfer device (CSTD) if necessary”, and stating that, “if use of a specific CSTD is required, the sponsor should provide it with the drug.”

#### WHAT CAN DRUG DEVELOPERS DO TO ENSURE SAFETY FOR HEALTHCARE WORKERS?

Given the uncertainty in handling new clinical trial-stage drugs, it is vital that drug developers are partnering with reliable, clinically evaluated and proven safety equipment. Only those products that have proven their efficacy to the strictest standards will provide the protection to both healthcare workers and trial participants.

Those working in drug development can ensure they are achieving the highest safety levels for handling investigational drugs by partnering with CSTD-makers who are willing to work closely with the pharmaceutical industry early in the drug development process to understand system feasibility. Furthermore, drug developers should look for a partner willing to develop customised solutions to address their unique needs.

#### INVESTIGATIONAL DRUGS AND PATIENT SAFETY

When investigational drugs reach Phase I, in which they are administered to humans for the first time, maintaining sterility from manufacturing through to administration is critical not only for worker safety, but especially for patients. Patients utilising investigational drugs, either in trials, or through expanded access for those with severe health conditions that have exhausted other options, are often immunocompromised. As such, adhering to current good manufacturing practices (cGMP) is key for all personnel involved in trial phase investigational drug handling.

To ensure aseptic drug processing, drugs should be handled under laminar flow hoods, biosafety cabinets or using isolators. Further, having appropriate air flow during compounding can help ensure that the drugs remain sterile and isolated from the environment. Microbial control is also a key component of drug sterility and safety. This is another element for which a clinically-validated CSTD may serve a key role in the future. CSTDs that mechanically prevent the transfer of environmental contaminants into the system can prevent microbial ingress and protect the sterility of the drug. Given the state of patients trialling such drugs, any introduction of an external contaminant could skew results of the drug’s efficacy, and potentially harm the patient. As such, all available means of maintaining the drug’s sterility should be implemented, from environmental controls to engineering controls, including CSTDs.

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## THE FUTURE OF SAFE HANDLING FOR INVESTIGATIONAL DRUGS

With the uncertainty surrounding the safety of investigational drugs, regulations will only become stricter and healthcare professionals will continue to demand better and proven safety measures. As in the hazardous drug handling industry, the use of CSTDs looks set to become the norm. This means that now is the time to begin assessing current systems on the market. Just as drug developers must critically assess the safety and efficacy of the medications they are developing, so too should they look to select a closed system that has been

rigorously tested and proven effective at minimising the risk of hazardous exposure. Doing so will allow developers to move past compatibility issues early, and find new, customised ways to offer an ideal drug delivery product that is safe for healthcare professionals and patients alike.

### ABOUT THE COMPANY

Equashield is a leading provider of manual and automated solutions for the compounding and administration of hazardous drugs. Equashield's product suite includes EQUASHIELD II, its flagship closed system transfer device (CSTD), and EQUASHIELD®

Pro, the first ever closed system-enabled automated pharmacy compounding system (APSC). Equashield's CSTD is clinically proven to protect healthcare professionals from hazardous drug exposure. EQUASHIELD II covers more routes of exposure than alternative systems and has passed the proposed 2015 alcohol vapour containment protocol from NIOSH, confirming that it can contain the harshest vapours and emissions. Studies have demonstrated that Equashield's CSTD is faster to deploy and easier to use than competing systems. Used by hundreds of hospitals and clinics around the world, EQUASHIELD II is CE marked and substantiated by the US FDA for preventing microbial ingress for up to seven days.

### REFERENCE

1. Forshay CM et al, "Application of the 2015 proposed NIOSH vapor containment performance protocol for closed system transfer devices used during pharmacy compounding and administration of hazardous drugs". *J Oncol Pharm Pract*, 2018, epub.

## ABOUT THE AUTHOR

Marino Kriheli, Co-Founder of Equashield, has over twenty years' experience in industry project management, in both the industrial engineering and medical device manufacturing spaces. In 2010, he co-founded Equashield, a leading provider of a full range of manual and automated solutions for the compounding and administration of hazardous drugs. Prior to founding Equashield, he co-founded medical device manufacturer Plastmed, an original equipment manufacturer for Johnson & Johnson.

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