

## Minimizing human intervention in intravenous admixture practice

DENNIS A. TRIBBLE

Am J Health-Syst Pharm. 2010; 67:389-90

I recently read a commentary by Agalloco et al.<sup>1</sup> regarding aseptic manufacturing. It reinforced precepts of *United States Pharmacopeia (USP)* chapter 797<sup>2</sup> and caused me to wonder about the evolution of the i.v. room as we know it.

The first point of wonder is that there was a time when aseptic manufacturing of commercial products involved the same kinds of activities we currently see in hospital pharmacy i.v. rooms. A photograph that Agalloco et al.<sup>1</sup> acknowledged only as being several decades old shows a completely manual aseptic manufacturing line. In contrast, today's aseptic manufacturing lines are typically completely automated, with little or no human interaction. As an "old timer" who made his first i.v. admixture in 1974, I can assert with some confidence that the general practice of i.v. admixture compounding has not changed substantially in over 30 years. In those same decades, the only improvements we have seen—with the possible exception of automated compounding of total parenteral nutrient solutions—involve automation of the way we produce labels.

The second point of wonder involves the Agalloco et al.<sup>1</sup> assertion that manual filling could no longer be considered good manufacturing practice because

1. Human intervention is the single most significant source of hazard in

aseptic filling, and primary engineering controls such as laminar-airflow hoods and biological-safety cabinets cannot sufficiently mitigate this hazard.

2. Manual preparation requires the human operator to be in intimate contact with the material meant to be kept sterile, and the frequency of human contact is unacceptably high (literally every preparation is handled by a human).
3. Human performance is not sufficiently reproducible to permit it to be predicted by normal validation methods, especially process simulation.
4. There are technologies available that can overcome the above-listed limitations.

By these arguments, the environments we try to maintain for manual dose production in hospital i.v. rooms are inadequate to their tasks. The only technology the authors deemed adequate was the use of isolators and restricted-access barriers that, while not completely removing the human-contact-based hazard, reduce it by orders of magnitude.

DENNIS A. TRIBBLE, PHARM.D., is Chief Technology Officer and Chief Pharmacy Officer, ForHealth Technologies, Inc., 790 Fantress Boulevard, Daytona Beach, FL 32114-1214 (dtribble@fhtinc.com).

The author is employed by a manufacturer of robotic equipment used in the preparation

The third point of wonder is that there are now technologies available that substantially eliminate human involvement, to the point that manufacturers now document every individual human intervention in an aseptic filling system, down to the identity of the person involved, because those interventions are the single most likely cause of an aseptic failure. The commentary closed with this: "The time is approaching to make hand filling in clean rooms a part of our history, something we used to do."<sup>1</sup>

Of course, this describes aseptic *manufacturing*, the preparation of those packages that pharmacists, in turn, use to prepare individual patient doses. However, it does appear that i.v. admixture practice is evolving along the same lines. As explained at the training for the most recent release of *USP* chapter 797,<sup>2</sup> the whole purpose of the chapter appears to be to better approximate for i.v. admixtures the kinds of controls applied to manual aseptic manufacturing. In that chapter, one finds the following quote: "Despite the extensive attention in this chapter to the provision, maintenance and evaluation of air quality, the avoidance of direct physical contact contamination is paramount."

This raises the question of how long we will continue to use primarily manual preparation methods for i.v. admixtures. As pharmacies at-

of sterile products.

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DOI 10.2146/ajhp090144

tempt to centralize functions to improve the use of precious pharmacist time, reduce cost, and improve the general level of performance, the line between admixture-as-compounding and manufacturing becomes blurred. Indeed, pharmacists in some parts of the world refer to their practices as “good *manufacturing* practices.”<sup>3,4</sup> What is clear is that there are a sufficient number of drugs with an extremely limited shelf life once prepared that the compounding of i.v. admixtures in hospital pharmacies will continue for the foreseeable future. The question arises, How will that admixture be prepared?

If we attempt to extend the concepts of automated manufacturing from the commentary by Agalloco et al.,<sup>1</sup> it would appear that automation of critical tasks within the admixture process is key for removing the opportunity for contact contamination. There are some notable caveats, however. The injectable containers currently used in hospitals are not designed for robotic use; they are designed for human use. One engineer I know described the injection vial as “automation-hostile.” Because vials are closed, rigid containers, moving fluid out of them using a needle requires complex venting procedures that significantly slow robotic performance. Nobody has yet successfully designed a mechanism for opening a glass ampul. All of these containers are low-precision articles that require an incredible amount of processing just to completely and accurately extract their contents. Further, the only mechanism currently available for extracting fluid from an injectable container is a hypodermic needle, which, too, is designed for human use. Currently available needles are neither perfectly straight nor reliably similarly crooked. Again, a robotic system has to perform a lot of processing just to get the needle tip in the right place. In addition, the quality of materials used in vial stoppers

is highly variable, as is the stoppers’ geometry. This affects the force, orientation, and position of the needle lumen relative to the geometry of the stopper to effectively acquire the vial contents. Similarly, i.v. admixture solution containers are designed for human, not robotic use. They have wide variation in placement and geometry and require penetration by a needle for filling. Further, pharmaceutical container filling has wide permitted variance; the powder fill for a vial intended for reconstitution can vary as much as 15% on average and up to 25% for individual fills.<sup>5</sup> As a result, a precise robotic device will regularly encounter containers that have more or less in them than it expects, with the result that the device performance will differ from human expectation.

Syringes used for preparations, while treated as quintessentially accurate, are actually permitted quite a bit of variance. The accuracy of a disposable syringe is governed by International Organization for Standardization standard 7886-1, which permits the most accurate syringe to have an accuracy of  $\pm 4\%$  when delivering more than 50% of the syringe volume.<sup>6</sup> This means, for example, that a 10-mL syringe that visually contains 10 mL of fluid may actually have 9.6–10.4 mL and still be considered accurate. Variances accrue both from variances in the inner diameter of the syringe and from variances in scale placement on the body of the syringe. This results in two issues: (a) use of disposable syringes in automated devices limits the available accuracy of the device, and (b) the filling into a syringe can be perceived as inaccurate when, in fact, it is the syringe, not the filling process, that is inaccurate. The result is that technologies that can handle the panoply of different input and output containers currently managed by i.v. rooms can barely emulate, much less surpass, human throughput and often gener-

ate more perceived waste than does human admixture. Industry accepts waste as a cost of doing business; pharmacies do not. Finally, there is no technology available that can handle every preparation.

As these technologies evolve, meeting and exceeding human performance while maintaining appropriate distance between human operators and the preparations themselves will require the creation of new sterile product packaging that is more amenable to robotic manipulation. In the meantime, let us learn from our colleagues in industry that humans are fallible and that the progression of our practice in this area will reach fruition only when we routinely remove human manipulation from the process and press for the creation of technologies and supportive packaging that permits automation to help us perform to the same level as manufacturers.

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