

## Risk Management, cGMP, and the Evolution of Aseptic Processing Technology

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At the 2008 PDA Risk Management in Aseptic Processing Meeting the audience was shown a series of photographs depicting aseptic processing over the years. Among the photographs shown, none was more attention-getting than a shot from several decades ago showing a number of technicians hand-filling syringes (see Figure 1).

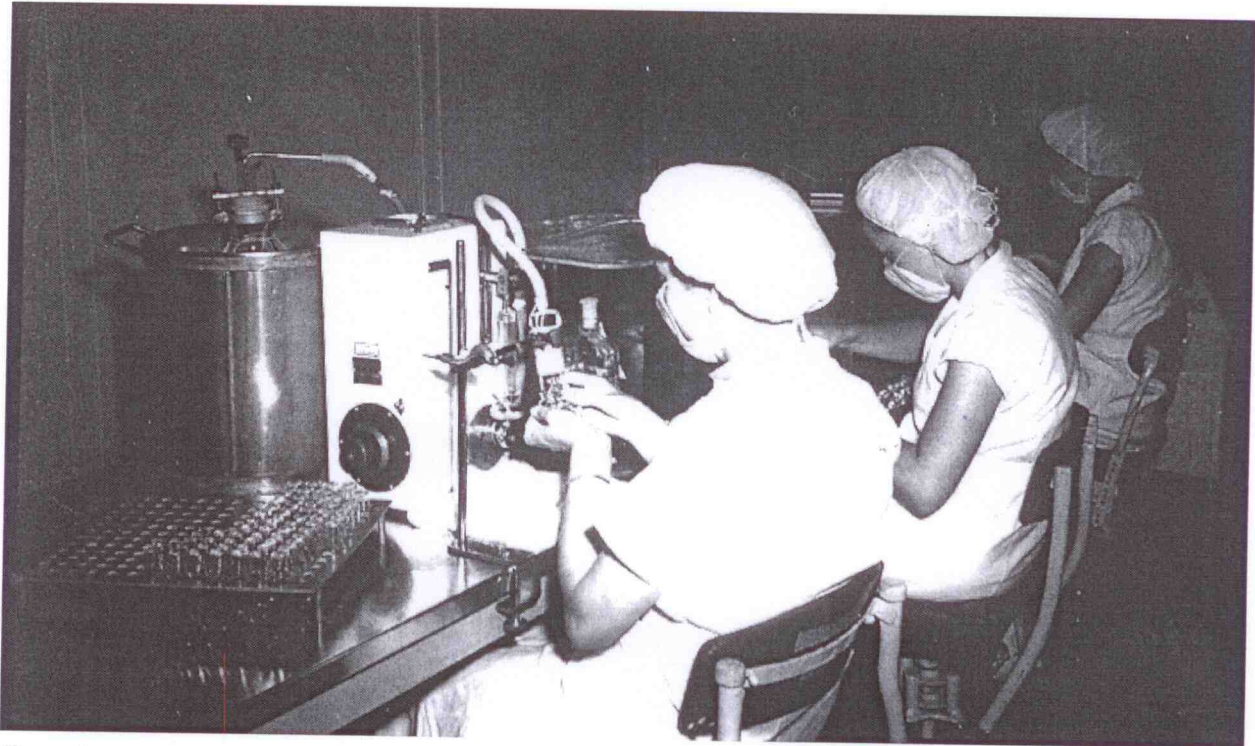
The fact that the technicians were in short-sleeved scrub suits certainly added to the shock, but we believe many people at the meeting found the hand filling alone difficult enough to accept. Individually and collectively, the authors of this paper made another observation. In all too many ways this old image resembled too closely present day practices for small batch manual aseptic filling by gowned operators.

It is inevitable that at a meeting devoted to risk assessment and mitigation in aseptic processing that filling technology would be a central discussion topic. In fact, technology, be it analytical or manufacturing, was a common thread that ran throughout the meeting. A fundamental technology question emerged: will or perhaps should some of the presently accepted aseptic processing technologies fall by the wayside as substantial improvements in available technology continue? In the jargon of our industry, this question can be re-phrased: are any of our current aseptic processing technologies no longer current good manufacturing practice (cGMP)? Although it was unlikely that full consensus would be reached by all present, the opinion expressed by many was that non-cGMP status for older aseptic process technologies is perhaps inevitable; the only uncertainty is the time when that would occur.

*Practice*, as in *good manufacturing practice*, or in the much newer phase *best practice*, is a word fraught with meaning in our industry. In the cGMP context it has significant legal meaning, as a failure to comply with cGMPs is in fact a violation of the law. Since the origination of this legal requirement, the “c” (for *current*) was placed in front of GMP to convey the reality that the GMPs were not static and that there is an interpretive element to these regulations (1). This is logical because the cGMPs like the current guidance on risk management are intended to be non-prescriptive. That is, they provide direction regarding “what” rather than “how”. More recent regulatory guidance such as ICH Q8, 9, and 10 as well as the FDA’s Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations accentuate this philosophy (2–5).

There are, of course, aspects of the cGMP regulations directed toward the control of microbial contamination. The specific control practices to be utilized are not stipulated but rather are left to each firm to determine “how” they will comply with the need for microbial contamination control. The “c” in cGMP does not imply the need for adaptation of state-of-the-art technology, which in our rapidly evolving field can be excruciatingly difficult to define. The “c” does, however, imply that the technology and systems used by a firm are current enough to mitigate unacceptable risks and that the firm is not relying solely on technology or approaches that are no longer able to provide the appropriate level of risk mitigation.

The authors believe that hand or manual aseptic filling in cleanrooms is one technology nearing the end of its justifiable use. It is extremely difficult to establish a



**Figure 1**

**Hand filling of syringes.**

risk- and science-based argument for this technology that assures sufficient patient protection. Lacking such assurance, one has to question whether hand or manual aseptic filling operations can be considered current, which is to say cGMP?

Manual aseptic filling conducted by aseptically gowned employees in a unidirectional flow cabinet (often incorrectly called a “laminar flow hood”) in a clean room has numerous shortcomings with respect to safety that cannot be easily overcome. The following outlines the reasons why we believe this technology should be voluntarily eliminated:

1. It is well known that human interventions by gowned operators represent the major cause of risk to maintaining sterility and hence the greatest source of hazards and failures in aseptic processing (6–9).
2. The hazards created by operators may not be sufficiently mitigated in an environment as simple as a unidirectional hood or biological safety cabinet.
3. Hand filling requires the operator to be in intimate contact with sterile items in a manner inconsistent with the precepts of aseptic technique.
4. Operator practices have inherent variation and inconsistency that preclude the reproducibility provided by mechanical equipment.
5. Manual filling requires a frequency of contact with sterile items that greatly exceeds that of processing equipment. Each manually filled container is handled at least once; this is far more handling than is common with non-manual filling.
6. There are separative environmental control systems available that enable quick and relatively inexpensive conversion of hand filling to far less risk-intensive technologies.

The idea that human operators are the major, some would claim only, significant risk modality in aseptic processing is well accepted. It is accepted not only by nearly all contamination control experts, but also by

regulatory experts. Over the last two decades a central requirement in process simulation testing has been the inclusion of all interventions, both inherent and corrective. So concerned are we about the risk control associated with interventions that most firms keep records of interventions with respect to type, time of occurrence, and even the name of the person conducting the intervention.

The concern with interventions has also manifested itself in the design of aseptic processing technologies and components intended to reduce or even eliminate interventions altogether. Recent decades of aseptic processing technology evolution are filled with examples of intervention elimination. Among them are CIP/SIP (clean-in-place/sterilization in place) to eliminate aseptic connections, in-line depyrogenation of containers, automatic weight-check, machine controls such as no container–no fill, improved component handling, electronic adjustments, automatic lyophilizer loading, and equally significantly separative technologies.

Separative technologies, such as isolators and restricted access barriers (RABS), are designed to minimize environmental risk in general and intervention risk specifically by separating the operator from the aseptic processing critical zone, or area of highest contamination risk. This critical zone is where product and primary packaging components are brought together and assembled into a drug, biologic, or device. Closed isolators, that is, isolators with no direct opening to the surrounding room and which do not allow for any door opening to allow for direct operator access, are the pinnacle of modern aseptic processing risk abatement. This does not mean that some residual aseptic processing risk does not persist in isolators; however, most experts believe the risk is conservatively 1:100–1:1000 less than in a conventional clean room with gowned operators. Certainly, data collected over the now nearly two decades of experience with production isolators supports this risk abatement contention.

These newer aseptic processing environmental control technologies are currently available and completely suitable for small-scale filling operations. These newer technologies are neither overly complex nor expensive, and are wholly compatible with manual activity (on a par with handling in sterility test isolators). They

are, however, decidedly more capable in eliminating or significantly mitigating the hazards of manual filling. Therefore, companies using manual filling should critically assess the hazards of their current manual processes in unidirectional hoods and biological safety cabinets and compare them to the available alternatives. The time is approaching to make hand filling in cleanrooms a part of our history, something we used to do.

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