

## Current Challenges in the Manufacturing of Injectable Drug Products

Mohammad Shakil Siddiqui<sup>1\*</sup>, Ghulam Sarwar<sup>1</sup>

<sup>1</sup>Department of Pharmacy, Jinnah University for Women, Karachi-74600, Pakistan.

### INTRODUCTION

The manufacture of injectable pharmaceuticals presents challenges from many perspectives, especially for products that must be processed aseptically and cannot be terminally sterilized. Food and Drug Administration (FDA) inspections for Good Manufacturing Practice (GMP) compliance in injectable drug product manufacturing facilities commonly find problems in the following areas:

#### ISSUES WITH ENVIRONMENTAL CONTROL PROBLEMS WITH EQUIPMENT, ESPECIALLY OLDER EQUIPMENT

Media fill failures and/or issues with media fills truly simulating actual practices

- Lack of proper training of operators
- Documentation failures

Besides the need to be in GMP compliance, manufacturing requires competency and resiliency in such matters as: inventory management, scheduling of facilities, equipment and personnel, management of changes in schedule, management of shutdowns for maintenance and repairs, management of change control, management of changes in product demand and departmental growth.

It takes well-organized and competent management and highly trained and competent operators and manufacturing support personnel to deal with all these challenges successfully. This article will focus on a few of the challenges involved in the manufacturing of injectable drug products - the process, equipment, people and environment.

\*Corresponding author: mshakil@hotmail.com

### PROCESS

Unit operations in sterile product processing include: compounding (or formulation), mixing, homogenization (dispersed systems), filtration, filling, stoppering, sealing and terminal sterilization (although a significant majority of small volume injectable products cannot be terminally sterilized for stability reasons). All segments of the manufacturing process present many challenges, especially as the process is scaled-up from bench to full production.

The pathway of a process is usually initially defined in a lab setting at small-scale by scientists who are frankly not highly experienced in the world of manufacturing. Some process methods are simple activities, such as weighing and mixing, while others are more complex and require special procedures, equipment, temperature control, inert atmospheres, protection from light and explosion proofing. Special criteria must be considered during the transfer of a process from the development lab to the manufacturing environment. Ideally, processes should be designed to be transferable on multiple projects in order to maintain a key principle in quality manufacturing. That principle is consistency for the manufacturing of sterile injectable products, consistency is critical. It is well known that media fills are only a snapshot in time, and merely demonstrate that under the 'correct conditions', aseptic filling of solutions is possible for that particular filling line.

More importantly, however, is the fact that we base the entire principle of media fill validation on the ability, and expectation, to consistently perform each operation in the same quality manner for each and every batch. These 'correct conditions' include the

proper environment, equipment, components, personnel and process methods.

### **EQUIPMENT**

Many challenges posed by manufacturing process methods can be solved by the proper choice of equipment. However, applying proper equipment always has a price. Once the initial cost of the equipment is considered, then come installation and validation issues. It is imperative to consider space and utilities required before getting started. Once in place, the company budget must be prepared to support a preventative maintenance programme, including a sufficient spare parts inventory. There is nothing more frustrating than loss of production due to equipment failure and worse, not having the means to repair or replace the parts necessary to resume manufacturing. During annual budget planning sessions, it is important to balance the push for cost reduction and optimization with robust processes and capable equipment-support programmes.

Once the right equipment has been sourced for the process, proper identification and control for all product contact parts is vital to quality manufacturing and preventing the risk of cross contamination. Elements of this challenge include the handling, cleaning, testing, release, storage, issuing and return of each product contact part. Furthermore, the importance of each of these areas is easily confirmed by the fact that they are frequently primary auditing targets.

### **PEOPLE**

Some may believe that people are the source of most, if not all, problems encountered in manufacturing, particularly aseptic manufacturing. In fact, the development of isolators and automation is driven primarily by the desire (and possibly need) to remove people from direct contact with sterile products during manufacturing. The root cause, however, may be better correlated to how the people are developed.

Training and experience are the primary solutions to minimizing or eliminating operator errors.

### **TRAINING**

A strong training programme is essential in the manufacture of pharmaceutical products. Training must be well organized to effectively maintain the compliance of all operators, who must be trained on the most current versions of all applicable standard operating procedures (SOPs). A solid change control process for procedures is required to properly maintain compliance with operator training. Training curricula are helpful tools that outline all SOP training and qualifications required for each position. These curricula are a valuable reference for auditing, and an easy way for operators and management to measure their development over time.

### **EXPERIENCE**

Most manufacturing operations are SOP-driven and are not conducive to classroom training for new operators. Job shadowing, with repetitive SOP review and hands-on demonstration, is the most direct method of transferring knowledge to new operators. For this reason, it pays in large dividends to develop experienced operators into effective trainers by investing in courses on effective communication and training techniques.

Experienced operators are not automatically the best trainers, but most can become quite capable with proper guidance. It might seem obvious, but new operators should always be paired with the most experienced operators/trainers. Furthermore, they should remain paired with the same trainer for as long as possible. It takes some time for a trainer to assess the trainee's strengths, weaknesses and rate of learning, then adopt the best pattern to use in each training opportunity. For example, some trainees may require more verbal repetition, hands-on practice, demonstrations, or SOP review.

Consequently, successful trainer/trainee teams will more efficiently and effectively work their way through all procedures on a training curriculum. A

strong training programme is also imperative for a fast growth rate in personnel, which can introduce a large number of new operators into the manufacturing operations at the same time. Any operation saturated with inexperience will likely incur an increase in errors. Again, this can be managed by pairing the new with the experienced.

### **ENVIRONMENT**

The impeccable quality of manufacturing environments for pharmaceutical processing is vitally important. We routinely measure the suitability of these environments with a variety of testing methods. The air is evaluated for direction of flow, velocity, pressure differentials, control of temperature, humidity, non-viable and viable particle content. Room and equipment surfaces are evaluated for general debris, microbial contamination and chemical contamination.

As people and equipment are part of the environment during the process, monitoring must be performed under dynamic conditions. The operators are also monitored for proper gowning and handling techniques using media contact plates in the search for microbial contamination at multiple bodily sites, such as chest, forearms, hands and fingertips. To meet the challenging specifications for environmental monitoring, the manufacturing operations must include proven methods for proper room clearance, cleaning and sanitization. Additionally, the gowning and cleanroom behaviour techniques must be both well trained and well practiced.

### **BATCH DEVIATIONS**

At some point, the challenges of manufacturing injectable products will eventually lead to some sort of batch deviation or variance. Batch deviations are typically due to a planned change or loss of control in at least one of the 'correct conditions' as discussed in this article. Some common root causes for deviations include: documentation errors, equipment/software problems, product/material defects, performance errors and incorrect process

methods.

It should be noted here that the above challenges with respect to people and environment have generated great interest and progress in the area of isolation technology. Successful application and validation of isolators enables the manufacture of sterile products to be distinctly separated from the direct intervention of personnel and ideally provides a safer environment for sterility assurance. However, beyond the scope of this brief article, there are many obstacles in the validation and routine use of isolators in aseptic manufacturing.

### **CONCLUSION**

We hear the common 'buzzwords' such as cost reduction, optimization, efficiency and capacity utilization. In our efforts to meet these goals it is important that we do not swing the pendulum too far from some other key manufacturing principles, such as training, practice, validation, preventative maintenance and availability of spare parts. It is important to find a balance among all these needs to meet the many challenges of manufacturing injectable pharmaceutical dosage forms.

### **REFERENCES**

- Remington's Practice of Pharmacy vol.1
- ICH guidance for Industry Q2B Validation of Analytical Procedures
- FDA Code of Federal Regulations