PRACTICAL ASEPTIC PROCESSING: FILL AND FINISH
VOLUME 1

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Part Two: Current Aseptic Processing Techniques

PREFACE

Irving J. Pflug

The manufacturing isolator, as it is used in 2009, is the culmination of perhaps, 60 years of developments in the microbial control of the sterile products manufacturing environment.

Equipment developers Al Larson and Jack Lysfjord of TL Systems Corp. were forward-looking innovators, who in 1985 had a vision that they could install a manufacturing line in the already proven glove-box containment system. Working with Hans Melgaard of Despatch Industries Inc., an expert in HVAC and particulate control in air systems, they developed a system where containers were fed from a washer and continuous sterilization–depyrogenation tunnel directly into a fill finish isolator system where high efficiency particulate air (HEPA)-filtered air was used to pressurize the system.

The microbiology quality of injectible pharmaceutical products produced in the 1950s clean room was of continuous concern.

Knowledgeable operators recognized that the microbiological quality of the products produced in the 1950s clean room system was related to the human operators in the clean room — the human in the clean room was the source of the contamination. Control measures were taken, starting with gowns, hair coverings and masks, then a full bunny suit; however, the human was still in the clean room.

The leap forward in control was moving the barrier from the operator to the production line. Instead of putting coverings (bunny suit) on the individual and trying to contain the microorganisms within a bunny suit (to keep them from escaping to contaminate the manufacturing area), the barrier was placed around the production line with the human operator outside the enclosure or isolator. This was a positive, controllable approach to solving the problem of the microorganism shed by the human operators from contaminating the product being packaged.

The availability of air, essentially free of microbial contamination, is a critical component of the isolator system. Today the development of the HEPA filter, laminar/unidirectional flow clean room system is often taken for granted and assumed by the young to have always existed. This system was developed with the support of the National Aeronautical and Space Administration (NASA) for producing higher levels of quality in intricate space vehicles (basis for the important original U.S. Federal Standard 209 which has recently been superseded by ISO 14644), and is one of the more import and recent technological advances that has helped the pharmaceutical industry in many ways. The HEPA filtered clean air is a critical part of the manufacturing isolator system.

The isolator itself will prevent microbial ingress, however, a method of decontaminating the isolator is a basic requirement of the manufacturing isolator system. We have been able to sterilize biological material, media and hardware, primarily using saturated steam under pressure for 100 years. We have been using ethylene oxide (EO) for sterilization for 50 years. Neither of these agents is suited for the isolator. The isolator is a large enclosure, not readily suited for one atmosphere of over pressure, and it requires human operators to work intimately with the system. Hydrogen peroxide (H_2O_2), an old chemical with many important attributes, has become the sterilant of choice for the manufacturing isolator system. We are surprised that, in recent years, it has not received very much attention in the microbial-control area. The oxidizing capacity of H_2O_2 is so strong that the chemical is considered a highly reactive oxygen species. It is used extensively in the pulp and paper industry. The FDA has classified H_2O_2 a low regulatory priority (LRP) drug. A 3% solution is sold as an over-the-counter drug and is used for cleaning wounds and as an oral debriding agent.

Hydrogen peroxide is used to decontaminate the manufacturing isolator in an air–H_2O_2 system or in an atmospheric steam–H_2O_2 system. In the atmospheric steam–H_2O_2 system at 100.0°C, the kill of *Geobacillus stearothermophilis* spores is faster than in saturated steam at 15 psi pressure and 121.1°C.

The pharmaceutical manufacturing isolator is an engineering system which is capable of high production rates of products with both high quality level and at a unit cost not heretofore possible. As pharmaceutical products become more

potent and more hazardous to healthy individuals, operators must be protected from harmful agents. Isolators are one of the best engineering solutions for protecting both the product *and* operator. This represents a giant leap forward from the manufacturing systems in use only 20 years ago.

INTRODUCTION

Jack Lysfjord

The seed for this book was planted in September 2005 at the PDA/FDA meeting in Washington D.C. Amy Davis, publisher of this book, and I were discussing how aseptic processing had changed since the mid 1990s.

Regulations have certainly changed with ISO 14644 cleanroom standards, 2004 FDA Aseptic Processing Guidelines, revision of Annex 1 of EU GMPs and International Council on Harmonization (ICH) working toward better global alignment of regulatory issues between countries.

Aseptic processing technology had changed with the use of Advanced Aseptic Processing techniques, such as blow/fill/seal (BFS), isolators and Restricted Access Barrier Systems (RABS). I believe that the product contamination rate can be improved from 1 contaminated unit out of 1,000 with conventional cleanroom processing to 1 out of 1,000,000 or even 1 out of 10,000,000 with the proper use of these advanced aseptic processing techniques. Conventional cleanroom processing has an inherent risk of human operators shedding of particles with viable micro-organisms into the containers.

Validation philosophy has evolved with the 5th edition of Good Automated Manufacturing Practices (GAMP 5). It is truly better understood today by industry as well as regulators. Process Analytical Technology (PAT), Quality by Design (QbD) with ICH Q8 (pharmaceutical development), Q9 (risk assessment) and Q10 (quality systems) tying things together for a better controlled process.

Products are changing with the increasing dominance of biologicals and biotech products including vaccines. Several large, well established pharmaceutical companies (over 100 years old) have now declared themselves to be “Biotech Companies”.

Today, more products are being produced that have a containment requirement, such as cytotoxics, to protect operators of process equipment and nurses who administer drugs to the patient.

Manufacturing of clinical trial material is a growing critical phase of aseptic processing as is the compounding of sterile preparations.

The rate of change is increasing rapidly. I felt as a contribution to newcomers to the industry, the seasoned person in operations, engineering or quality, pharmacists and regulators, that this book would draw a line in the sand for 2009 as to what is being done at this point in time. Current Good Manufacturing Practices (cGMP) are the current “state of the art”. We all need to stay on top of “what is current?”.

To limit the scope of this book, it will deal with manufacturing aseptic products until the container is closed, inspected and can be placed into “in process inventory” under quarantine. It will not deal with the downstream operations that involve “paper products” such as labeling, cartoning, casepacking etc.

I have worked hard to assemble a global group of authors for chapters that are experts in their particular topic to share their knowledge with you. I hope this information will be valuable for years to come.

Jack Lysfjord
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  - Irving J. Pflug, University of Minnesota, Allan Larson, president, TL Systems and Hans Melgaard, VP Technology, Despatch Industries

- Bob Best, president, ISPE who took on the idea of barriers and isolators
- Two pharmacists who help me see through their eyes:
  - Berthold Duethorn and Tom Jeatran
- Some of the regulators who helped advance the technology of aseptic processing:
  - Terry Munson, Ken Muhvich, Peter Cooney, Bob Sausville and Rick Friedman

Life is a journey. Enjoy it! Live your Bliss!

Jack Lysfjord
Minnetonka, Minnesota, March 10, 2009

DEDICATION

I dedicate this book to the patients of the world! Everyone has been, is or will be a patient. I hope the contents of the book will positively influence the governments, regulators and the pharmaceutical and related industries to produce more, better, safer and more cost effective products to help patients lead a full productive life.